FDA Executive Summary

Prepared for the June 17, 2014 meeting of the
Gastroenterology and Urology Devices Panel

Premarket Approval
P130019

EnteroMedics Inc.
MAESTRO® Rechargeable System

Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

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1. ABBREVIATIONS

BMI: body mass index
CI: confidence interval
CEC: clinical events committee
EMC: electromagnetic compatibility
EMI: EnteroMedics Inc.
EWL: excess weight loss
ITT: intent to treat
LVCF: last value carried forward
MRI: magnetic resonance imaging
OUS: outside United States
PAS: post-approval study
PP: per protocol
RNR: rechargeable neuroregulator
SAE: serious adverse event
SD: standard deviation
TBL: total body weight loss
VBLOC: vagal blocking therapy
%EWL: percent excess weight loss
%TBL: percent total body weight loss

2. INTRODUCTION

The applicant, EnteroMedics Inc. (EMI), has submitted a premarket application (PMA), P130019, for the MAESTRO Rechargeable System. The purpose of this FDA executive summary is to present information relating to the safety and efficacy of the MAESTRO® Rechargeable System, an abdominal vagus nerve neuromodulator which delivers vagal blocking (VBLOC) MAESTRO® Therapy. Currently, there are no legally marketed vagal neuromodulation devices for treatment of morbid obesity.

Pivotal studies were conducted under the investigational device exemption (IDE, G070025). The PMA application includes information regarding the results of the clinical trials, as well as device design, preclinical data (including animal study data), and post market approval data collection plans.

This document provides a summary of FDA's review of the P130019, highlighting areas where Panel expertise is being solicited. It includes a brief description of the device, and an overview of the preclinical and clinical studies conducted by EMI. The advisory panel is being convened to discuss the clinical data collected to demonstrate safety and efficacy in support of PMA approval for this "first of a kind" device.

3. REGULATORY HISTORY

The PMA, P130019, has been reviewed by the Office of Device Evaluation, Division of Reproductive, Gastro-Renal and Urological Devices within the Center for Devices and Radiological Health of the Food and Drug Administration. A chronology of the key milestones with respect to this premarket approval application is provided below.

- **Prior to June, 2007** – Outside of U.S. Studies – EMI conducted an open label, non-randomized pilot study in 5 clinical centers outside of the United States (Australia, Mexico, Switzerland and Norway) to evaluate the safety and effectiveness of the MAESTRO radio frequency system (RF1).
- **July, 2007** – FDA approval of a pivotal study (G070025) for the EMPOWER clinical trial to study the MAESTRO™ Vagal Smart Modulation™ (VSMTM) System. The study was designed as a prospective, sham-controlled, randomized, double-blind clinical study to evaluate the safety and effectiveness of the non-rechargeable version of the MAESTRO System at 15 institutions and 300 subjects. The intended patient population was those who have a BMI >40 kg/m^2 to 45 kg/m^2 or $\geq$35 to 39.9 kg/m^2 with obesity related comorbidities. This system utilized the radio frequency MAESTRO System (RF2).
- **December, 2008** – FDA acceptance for modular PMA review of the MAESTRO RC2 System under M080021.

- **March, 2011** – FDA approval for the ReCharge pivotal study of the MAESTRO RC2 System at 12 institutions and 234 subjects. The trial was designed as a prospective, randomized, double blind, parallel-group, multi-center trial to evaluate the safety and efficacy of the device in treating obesity, with 12-month follow up in 233 implanted patients. The intended patient population was those who have a BMI 40-45 kg/m^2 or 35-39.9 kg/m^2 with obesity related comorbidities.
- **May, 2011** – First ReCharge subject implanted.
- **December, 2011** – Last ReCharge subject implanted.
- **July, 2013** – FDA filed P130019 for the MAESTRO Rechargeable (RC2) System.
- **September, 2013** – FDA issued a major deficiency letter that included concerns regarding the preclinical (bench) testing of the device; reporting of the 18 month data for the subjects enrolled in the study; and the clinical experience and training needs for the safety of device implantation and explantation.
- **November, 2013** – Applicant submitted response to the major deficiency letter.

4. PROPOSED INDICATIONS FOR USE

EMI proposes the following indications for use:

The MAESTRO Rechargeable System is indicated for use in weight reduction in adult patients with obesity who have a Body Mass Index (BMI) of at least 40 kg/m^2, or a BMI of at least 35 kg/m^2 with one or more obesity related co-morbid conditions, and have failed at least one supervised weight management program within the past five years.

Panel Question: The panel will be asked to discuss whether this Indication for Use is appropriate.

5. DEVICE DESCRIPTION

The MAESTRO Rechargeable System is comprised of three implantable device components, including a pulse generator (referred to as the MAESTRO Rechargeable Neuroregulator) which delivers electrical signals to nerve electrodes; and two electrical leads, which are placed on the abdominal vagus nerve trunks. The external components include a transmit coil, mobile charger and Clinician Programmer. The placement of the leads is depicted in Figure 5.1.

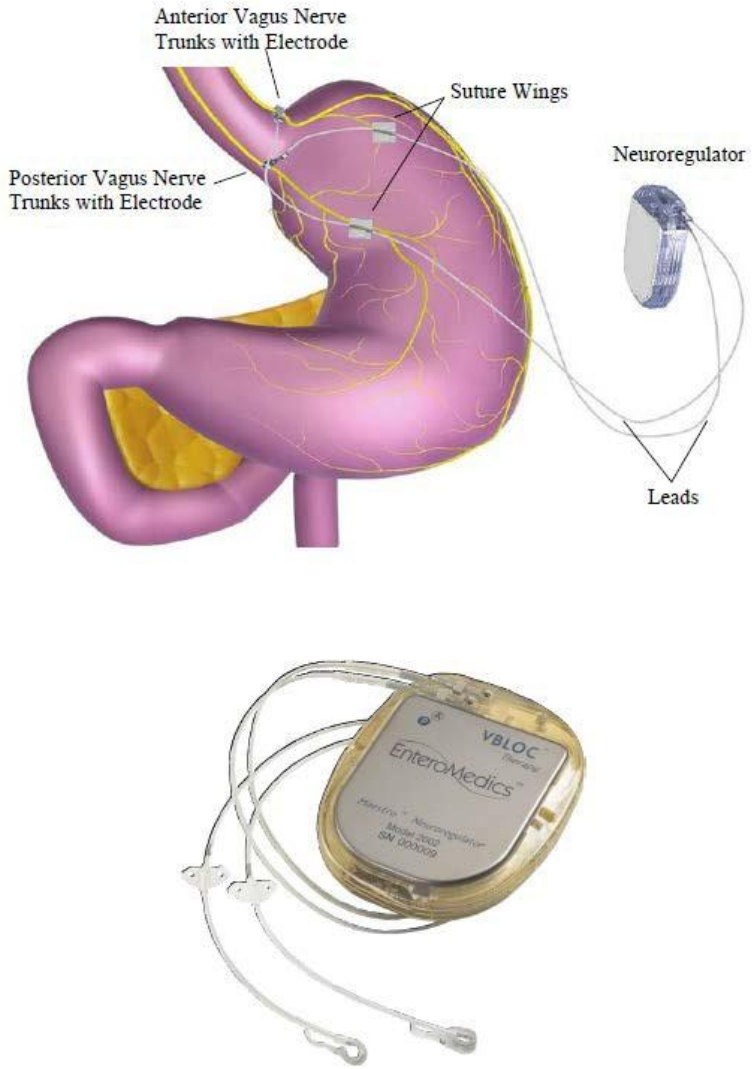

Figure 5.1. Electrode placement for the Maestro system.

The device components are further detailed on the following pages.

Model 2002 Pulse Generator (RNR)
This component has a hermetic case enclosure with an integrated coil that acts as the telemetry and recharging antenna. The RNR is surgically implanted subcutaneously on the thoracic sidewall. The principal function of the RNR is to deliver current to the leads. It contains a rechargeable 2.6 AH Li-ion battery (8 year battery life). It is recharged transcutaneously using the transmit coil. The RNR is labeled MR unsafe.

Model 2200-47E Leads (Anterior and Posterior)
These flexible leads are approximately 47 cm in length, and contain bipolar platinum/iridium tip & ring electrodes, with an insulated lead body. The tip (i.e., nerve) electrode contains rigid (316L) stainless steel encased in silicone to provide structural support. Current is delivered to the nerve electrode via 90/10 platinum/iridium electrodes. A suture tongue anchors and stabilized the nerve electrode. The tip electrode measures lead impedance and delivers electrical pulses to the vagus nerve trunks. The ring electrode is sutured to the stomach, and is used for measuring lead impedance. The leads are placed on the anterior and posterior intra-abdominal nerve trunks. Unlike the helical or closed cuff designs used with other peripheral nerve stimulation electrodes, the MAESTRO leads are described as being "C" shaped, and cradle rather than wrap around the abdominal vagus nerve trunks. Sutures anchor and stabilize lead placement.

Model 2402 Mobile Charger
This component is worn externally. It is connected to the transmit coil positioned over the RNR for recharging. It displays the operating status of the implanted device, and can be used by the patient to deactivate the device. Subjects were required to check the battery daily and recharge when needed.

Model 2403-60(A) Transmit Coil
This external component is placed over the RNR by the patient to charge the battery.

Model 2501 Clinician Programmer
This external component is a programmable, ambulatory microprocessor and controller with compatible, customized firmware. It is used by the clinician to modify therapy parameters and treatment schedule. It transmits information to the Mobile Charger and uploads data from the Mobile Charger.

Customized Software
Software is provided with the clinician programmer (CP)/ laptop computer, and enables communication with the mobile charger and neuroregulator. The CP allows physicians to modify therapy parameters and delivery schedules and retrieve diagnostic information.
Sample settings are set using the Clinician Programmer. Sample settings are depicted in Figure 2.

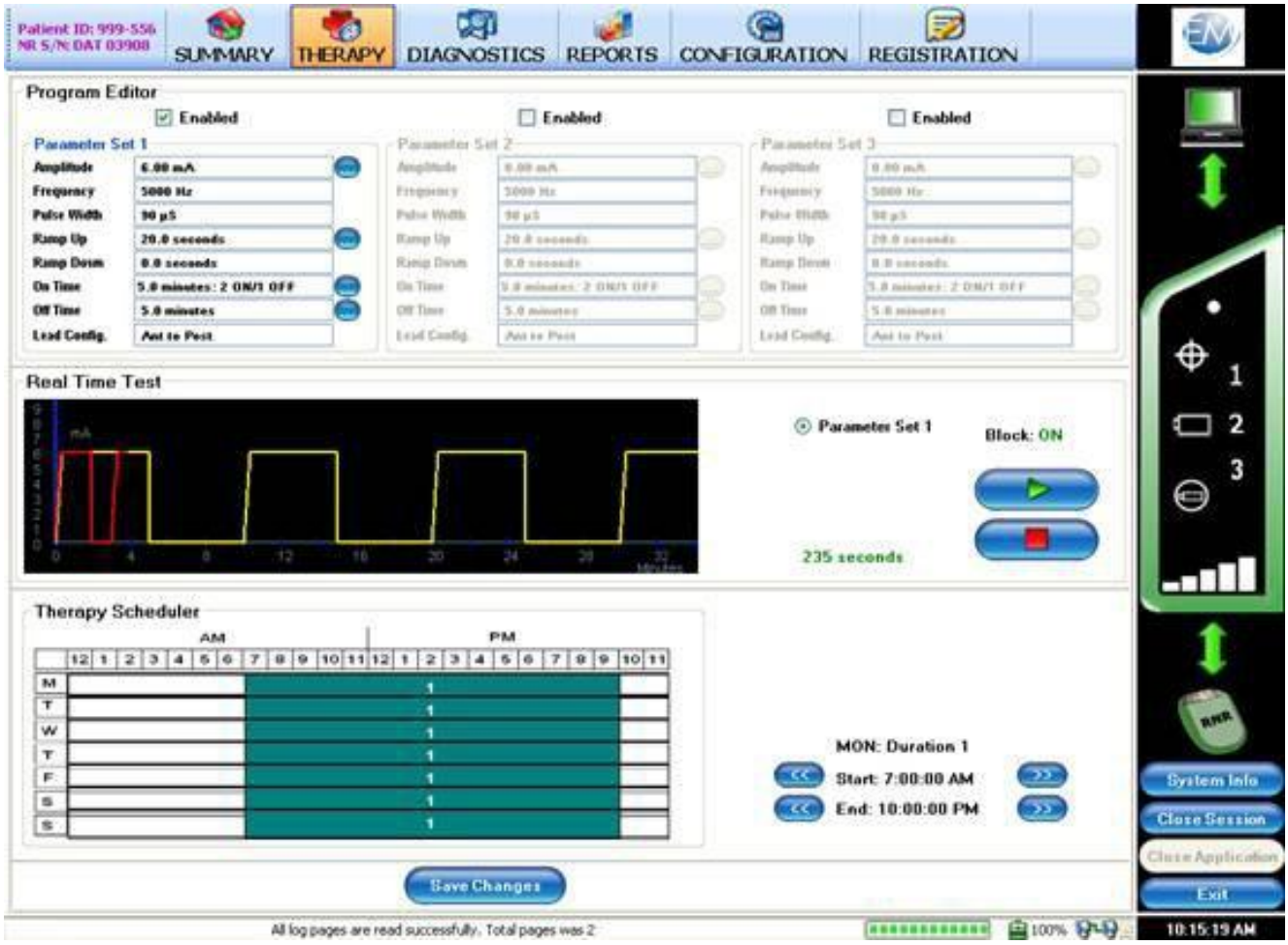

Figure 5.2. Screen shot of therapy options for VBLOC firmware.

A schematic of the arrangement of system components used to recharge the MAESTRO System is provided in Figure 5.3.

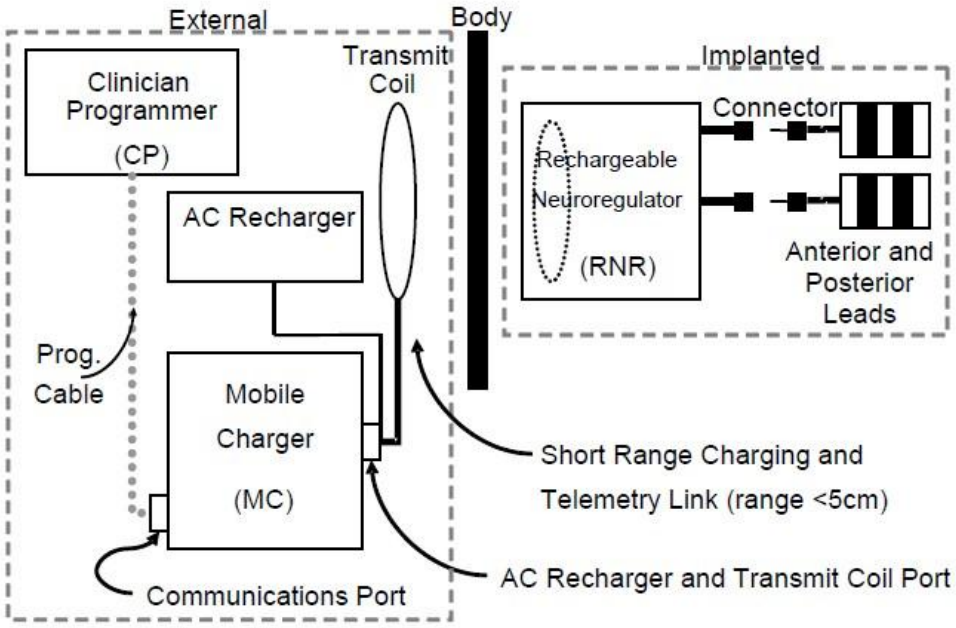

Figure 5.3. Schematic of implanted and external device components

Sham Device

Subjects in the sham control group did not receive the MAESTRO leads or electrodes, but were implanted with a nonfunctional sham: a neuroregulator which operates in the same manner as the functional neuroregulator. The neuroregulator's lead sockets are filled with medical grade silicone adhesive to ensure that no electrical current is delivered by the device. As with the active RNR, the sham RNR contains a battery. The sham has resistors that dissipate charge in a manner similar to the active neuroregulator, and thus requires recharging. Similar to the active group, sham control patients were required to recharge the battery.

Therapy Algorithms

The MAESTRO system is atypical of most medical "neurostimulation" devices, because it is intended to deliver pulses of current to vagal nerve trunks at such a high frequency that nerve activity is blocked, and the natural impulses that are conveyed from the periphery (i.e., stomach) to higher levels of the brain stem are suppressed. Table 1 provides the system specifications for VBLOC therapy (from Table 3-3, page 13, volume 1).

Table 5.1. Device specifications for VBLOC therapy.

	Specification	MAESTRO Recharge System
VBLOC settings	Frequency	5000 Hz
	Pulse width (µS)	90
	Constant current	0 – 8 mA
	Waveform	Square, biphasic, charge balanced
	Q (charge at 8 mA)	0.72 µC/phase
	Maximum charge density (8 mA)	5.3 µC/cm^2

A schematic of the stimulation waveform profile is depicted in Figure 5.4.

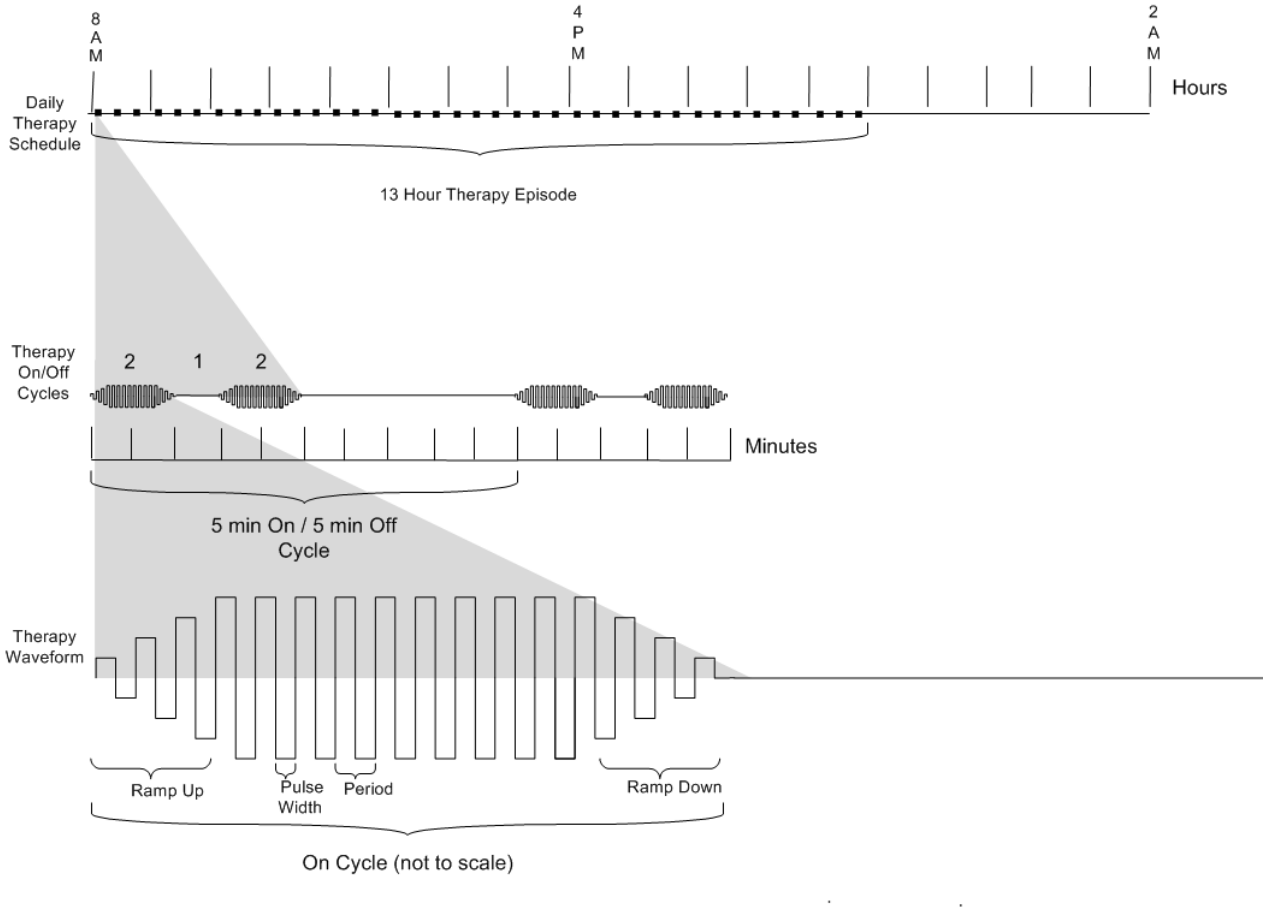

Figure 5.4. Schematic of the duty (ON/OFF) cycles for VBLOC Therapy.

Device Modifications

Modifications were made to the Clinician Programmer to address some usability issues that were discovered through clinical experience. The leads used in the ReCharge pivotal study are approximately 47 cm in length which is 12.5 cm shorter than the leads used with the EMPOWER RF device (page 95, volume 2). The lead re-design was intended to improve the safety of the leads. EMI is seeking approval of the 47 cm leads with this PMA.

Principles of Operation

The MAESTRO System is intended to reduce hunger pangs by applying electrical pulse algorithms which block signals to the anterior and posterior trunks of the intra-abdominal vagus nerve. Other intended weight-reducing effects of electrical neural blockade include:

- Reduced food intake by reducing gastric accommodation;
- Promoting satiety by delaying food processing and gastric emptying;
- Decreasing caloric intake.

Figure 5.5 illustrates the possible mechanisms of action underlying VBLOC therapy.

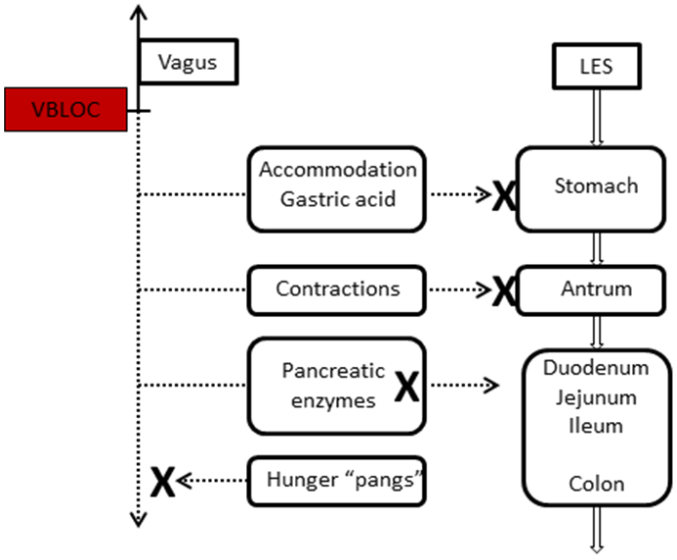

Figure 5.5. Vagus nerve blocking for obesity therapy.

6. CLINICAL NEED

Obesity is a major health problem that has dramatically risen in prevalence over the past 20 years. According to the Center for Disease Control, over one third of adults in the U.S. are clinically obese (**http://www.cdc.gov/obesity/data/trends.html**). The disease is characterized by overeating, excess adipose tissue, and is often quantified by body mass index (BMI). Obesity is a complex disease for which genetics, behavior, physiology, environment and culture combine as contributing factors. Chronic obesity contributes to other diseases, including cardiovascular disease, diabetes, obstructive sleep apnea, stroke, depression and cancer. Medical interventions have included pharmacotherapy (e.g., phenterminetopiramate, lorcaserin, orlistat), medical device implants (e.g., adjustable gastric bands), surgical interventions (e.g., gastric bypass, gastric sleeve surgery), and behavior modification. Currently, the most effective treatment for morbid obesity is gastric bypass surgery. Although an effective treatment, there are significant short- and long-term complications and adverse events, including perforations, hemorrhage, bowel obstruction, impaired nutrient handling, and surgical remodeling of the gastrointestinal tract.

It has been suggested that obesity is related to imbalances between satiety and feeding, which are regulated in part by gut hormones that communicate with neural centers, such as, the hypothalamus and brain stem, to provide visceral negative feedback, modulate body weight, energy homeostasis, metabolism and reward based behaviors. Hormones emanating from the gut and adipose tissue, such as ghrelin (the "hunger hormone") and leptin (the "satiety hormone"), interact with receptors that convey messages to the central nervous system, and influence anorexic or orexic behaviors[-5]:

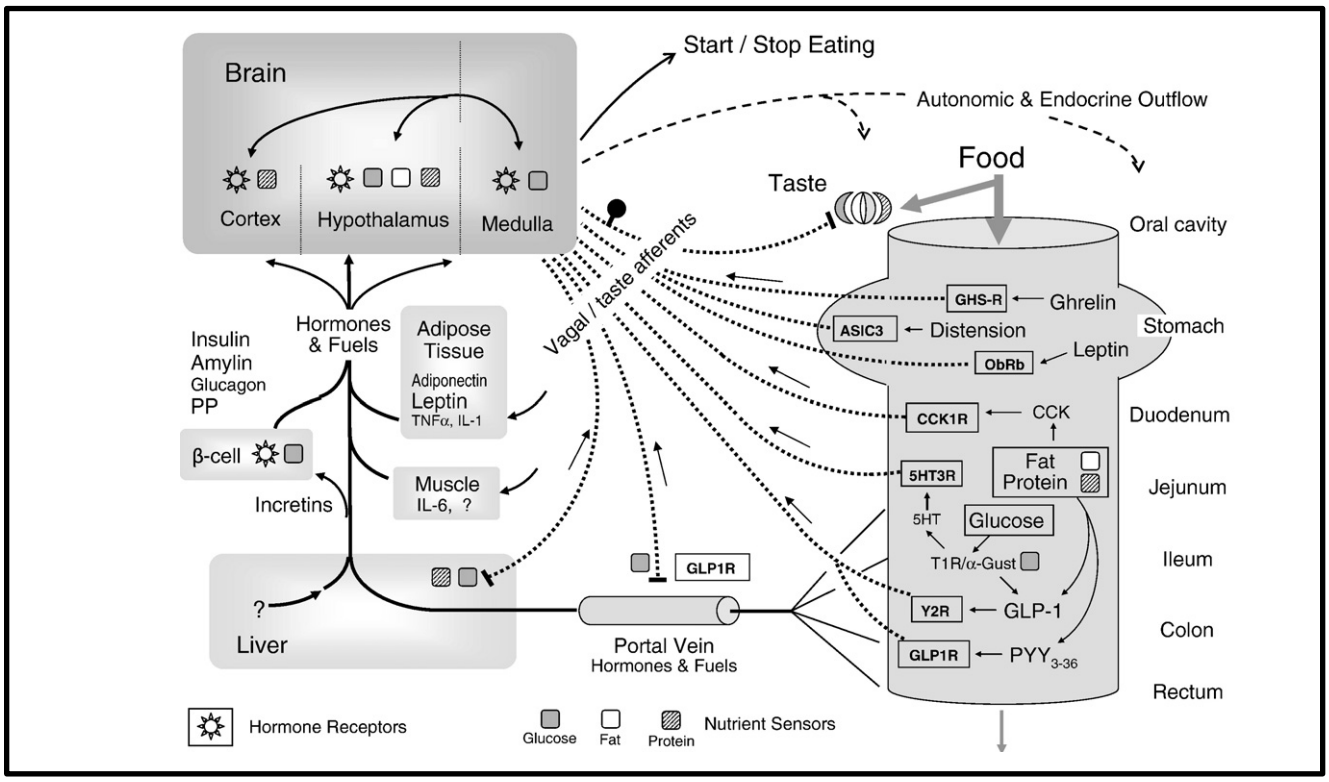

Figure 6.1. (text copied from Reference 7). Nutrient sensing in the alimentary canal and the control of food intake. Simplified schematic diagram showing the major pre- and postabsorptive transduction sites and mechanisms for the detection of ingested food and its macronutrient components. Nutrient information is sent to the brain through vagal and taste afferents (heavy dotted lines) or through the blood circulation (full lines). Specific receptors expressed by vagal afferent neurons are shown in rectangular boxes. Specific sensor mechanisms demonstrated for glucose, amino acids/proteins, and lipids/fatty acids are shown by gray, striped, and white squares, respectively.

There are myriad hormones and other biochemical mediators of feeding behavior that are part of the gut-brain axis, including peptide tyrosine tyrosine (PYY), glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM), glucagon, and vasoactive intestinal polypeptide (VIP). Preclinical testing has provided evidence that the stomach is a major source of ghrelin, and that ghrelin receptors are expressed on visceral afferents of the vagus nerve. Exogenous administration of ghrelin stimulates feeding activity, gastric acid secretion, and gastric motility. There are also animal and clinical data to suggest that ghrelin mediated effects are suppressed or abolished by vagotomy or pharmacological antagonism of vagus nerve activation [6-8].

Vagal Innervation of the Stomach

The gut-brain axis consists of a network of autonomic neurons that provide communication between myenteric ganglia (discrete packets of neuronal cell bodies) pocketed inside the muscle wall of the stomach; diffuse, intramuscular arrays; and neuronal axons that collect into nerve trunks, and extend processes to the brain stem. The anatomy and physiology of vagal, parasympathetic afferents to, and efferents from the stomach are complex. See for example, Powley's Figure 3, showing the network of dye-labeled vagal fibers of the rat which extend from the brainstem to the stomach wall [9].

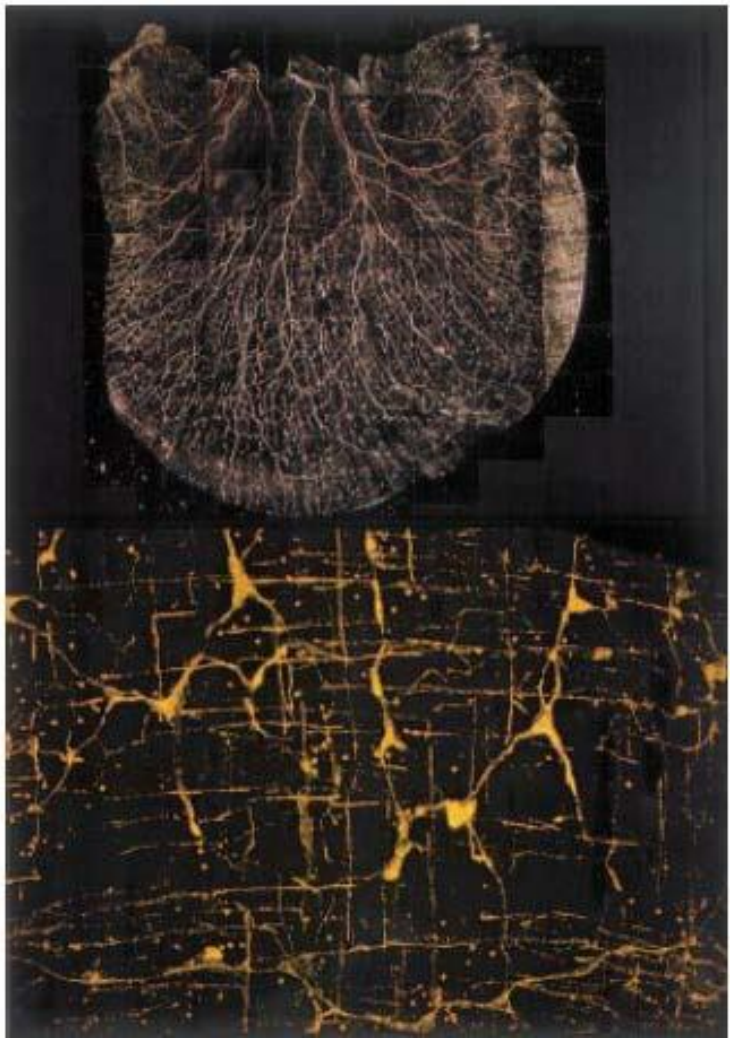

Figure 6.2. Upper panel: Montage of dye labeled vagal afferent or sensory fibers in the stomach wall of the rat, which were labeled with gold, wheat germ agglutinin-horseradish peroxidase. Lower panel: Higher magnification of vagal afferents, showing intraganglionic endings. From Reference 9.

A vago-vagal reflex controls gastric motility, tone and acid secretion via a reflex arc: The visceral afferents relay information along the abdominal nerve trunks about sensations of fullness, and the mechanical and chemical properties of food. This information is received by the brain stem and higher centers of the central nervous system. In turn, neural processing within the spinal cord suppresses the outputs of neurons that are responsible for maintaining resting gastric tone, and slowing down gastric motility [9]. Disrupting the vago-vagal pathways, either by electrical inactivation (e.g., via the MAESTRO Obesity Management System), or by surgical dissection of the abdominal trunks (i.e., truncal vagotomy) is reported to override the vago-vagal reflex, resulting in increased gastric emptying, and decreased nutrient absorption. Suppression of the abdominal vagal trunks may also alter the gut hormones that regulate hunger, satiety, and feeding behaviors, although there is currently no definitive evidence to demonstrate the biochemical cascades produced by vagal block.

From a historical perspective, truncal vagotomy has been a surgical option for treatment of peptic ulcer disease, and has been suggested as a surgical alternative to jejunoileostomy for treatment of obesity [10-13]. Complications of vagotomy of the abdominal nerve trunks include bowel obstruction, gastric stasis, diarrhea, and dysphagia. Other clinical observations in truncal vagotomy patients include increases in epigastric fullness and decreased hunger responses to exogenous ghrelin [13].

Measurements of Weight Loss

Body Mass Index (BMI), Percent Excess Weight Loss (%EWL), and Percent Total Body Loss (%TBL) are measurements that are often used to quantify the efficacy of various interventions for reducing weight in obese people:

BMI:

BMI = weight (kg)/height squared (m^2)

Ideal body weight is sometimes determined based on a BMI of 25 kg/m^2. A subject's ideal body weight can be converted to pounds , using the following formula:

Ideal Body Weight (lbs) = 25/703 x [height (in)]^2

%EWL: Percent of excess weight lost from baseline

%EWL = (weight loss/excess weight) x 100

where,

weight loss = baseline weight – weight at follow-up

excess weight = baseline weight – ideal body weight

Ideal body weight is commonly determined by using either the BMI method (described above) or the Met Life tables.

% TBL: Percent of total body weight lost from baseline

%TBL = (weight loss / baseline weight) x 100

Therapeutic Options: Direct-Acting versus Indirect-Acting Approaches

Studies on the efficacy of lifestyle interventions suggest that diet, exercise and/or counseling can produce modest reductions in weight (4 kg among obese patients, 2-9% total body weight) at the 12-24 month time point [14]. However, lack of patient compliance with lifestyle interventions often results in weight regain [14-15]. Methods for treating obesity that have near-immediate effects on food intake, such as gastroplasty and jaw-wiring, may provide unacceptable risk-benefit profiles in some patients. With increased scrutiny over the limitations of gastric bypass surgery, there is growing interest in alternative treatments for obesity, including the use of devices with indirect, potentially long term effects that modulate the visceral feedback from the hypothalamus [6]. However, treatments that have less traumatic, more subtle, but potentially long lasting effects (e.g., modulating visceral feedback from the hypothalamus) may require the implementation of effective short-term solutions for weight loss in order to form a physiological and/or behavioral link between short-term and long term changes in food intake. Powley et al., have noted that obesity therapies which target physiological systems that indirectly influence feeding behaviors can have long-term influences on weight loss; the effectiveness of such indirect approach can be undermined by more proximate influences (e.g., meal initiation triggered by exposure to nonhomeostatic signals, including environmental stimuli, ready food availability, and seasonal factors) [16]. These considerations could suggest that the effectiveness of EMI's VBLOC therapy may critically rely on early and direct interventions (e.g., behavioral modifications) that address the "non-homeostatic" signals presented to VBLOC patients.

7. PRECLINICAL STUDIES

Device Biocompatibility, Sterilization and Packaging

Device components are packaged and sterilized with ethylene oxide (EO). Validation testing demonstrated that the required level of Sterility Assurance Level (SAL) of 10^{-6} was met.

The 3 year shelf life assessed accelerated aging of device components. Compliance was confirmed by showing that each of the devices passed functional electrical tests after exposure to the accelerated aging conditioning. Shipping and temperature conditioning were evaluated in accordance with ASTM standards (ASTM D4169), and found to meet test criteria. Levels of residual EO and ethylene chlorhydrin in implantable device components also met test acceptance criteria.

The implantable components of the MAESTRO RC2 System, the bipolar leads and RNR passed the following biocompatibility and sterilization tests:

- Cytotoxicity
- Sensitization
- Intracutaneous reactivity
- Subcutaneous implantation
- Systemic toxicity, acute
- Systemic toxicity, chronic
- Sub-chronic toxicity
- Chemical characterization of extractables
- Genotoxicity
- Endotoxin levels with Limulus Amebocyte Lysate (LAL) testing
- Sterilization validation with process challenge device (PCD)
- Ethylene oxide residuals

Animal Testing

EnteroMedics evaluated the safety of implantation and nerve blockade of the porcine abdominal vagus nerve trunk. The device was tested using a variety of device components. An earlier design of the neuroregulator (Radiofrequency 2, or RF2) was tested with a 100% platinum electrode Model 1200 electrode. The tested device was revised to include an RF2 neuroregulator for use with a Model 2200 platinum-iridium electrode. A rechargeable neuroregulator was also evaluated in combination with the Model 2200 electrode.

A summary of the series of preclinical tests that were conducted using various models of the device components and therapy algorithms is provided in the following summary table. Note that pulse frequency was always maintained at 5000 Hz, and the duty cycle was always set to deliver 5 minutes of VBLOC therapy ON, followed by 5 minutes of VBLOC therapy OFF.

Table 7.1. Summary of porcine studies conducted on VBLOC therapy.

Animal Study ID	Study Year	Model# RNR; Model# Leads	Study Duration	Therapy Algorithm: Current (mA); Pulse Width (µS); VBLOC (Hours/Day)
TR01	2005	#1000 RNR; #1200 leads	1-3 weeks	2-4 mA, 100 µS; 12 hrs/day
TR02	2005	#1000 RNR; #1200 leads	4 weeks	2-6 mA, 100 µS; 12 hrs/day
TR03	2005	#1000 RNR; #1200 leads	8 weeks	2-6 mA, 100 µS; 12 hrs/day
TR04	2005	#1000 RNR; #1200 leads	12 weeks	4-6 mA, 100 µS; 12 hrs/day
TR05	2005	#1000 RNR; #1200 leads	1-3 weeks	6 mA, 100 µS; 12 hrs/day
TR06	2005	#1000 RNR; #1200 leads	12 weeks	6 mA, 100 µS; 12 or 24 hrs/day
TR07	2006	#1002 RNR; #2200 leads	9 days	6 mA, 90 µS; 24 hrs/day
TR08	2006	#1002 RNR; #2200 leads	4-12 weeks	6 mA, 90 µS; 24 hrs/day
TR09	2006	#1002 RNR; #2200 leads	12 weeks	6 mA, 90 µS; 24 hrs/day
TR10	2007	#1002 RNR; #2200 leads	4 weeks	8 mA, 90 µS; 24 hrs/day
TR11	2008	#2002 RNR; #2200 leads	4 weeks	6 mA, 90 µS; 24 hrs/day
TR12	2008	#2002 RNR; #2200 leads	12 weeks	8 mA, 90 µS; 24 hrs/day

Device components that are designed to be internally implanted during clinical trials include the neuroregulator and leads. For the animal studies, the neuroregulator and leads were exteriorized due to the anatomical limitations of using the porcine animal model. Exteriorization of these device components, and the natural growth of the animal subjects, resulted in chronic pulling forces that resulted in trauma to the nerve. The implantation sites are depicted in the following schematic:

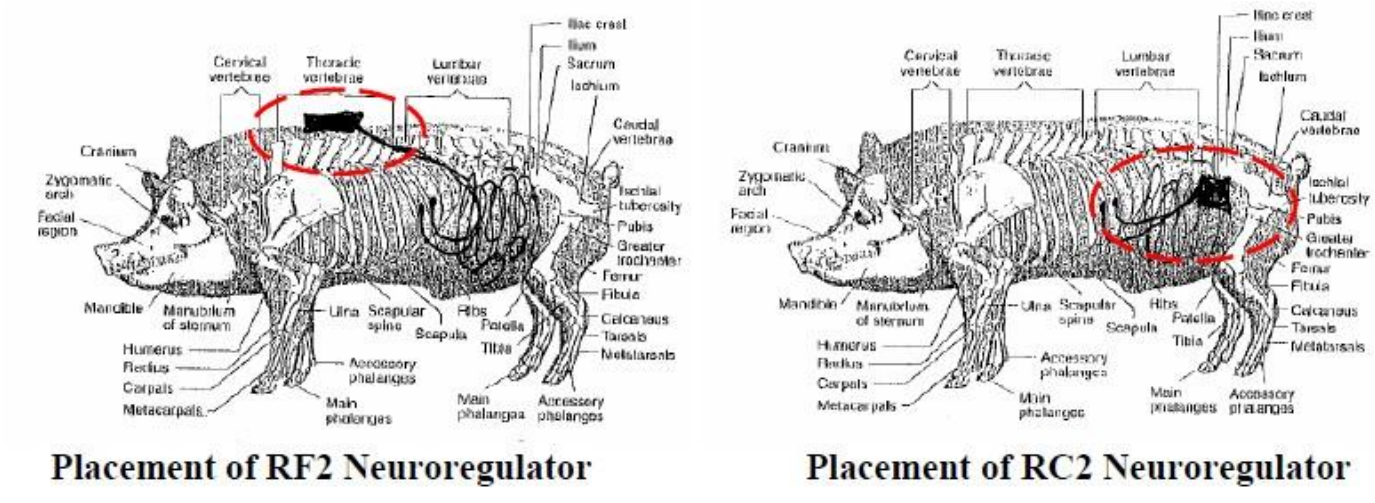

Figure 7.1. Depiction of device placement of the Maestro RNR and leads in pigs.

At the end of device implantation and therapy, the pigs were euthanized, and histological sections of the implant site were evaluated for evidence of neural injury. Micrographs of the tissue sections at or near the electrode implant site suggested that long term implantation could produce a moderate degree of early axonal degeneration. In one particular instance, evidence of tissue edema, mechanical compression and hyperplasia was interpreted as evidence of mechanical stress due to exteriorization of the leads.

Analysis: Exteriorization of the neuroregulator and leads was reported to produce neural trauma which likely exacerbated the neurodegeneration observed in histological sections of the implanted nerves. Therefore, the data provided by EMI may not have been representative of the long term safety of device implantation in humans. Further, the safety data from OUS and US clinical trials, including a relatively low rate of vagus nerve-mediated adverse events, suggest that the human experience with the MAESTRO system was more favorable than the animal data would have predicted.

Engineering

The MAESTRO System was evaluated for electrical and mechanical safety, electromagnetic compatibility, wireless technology, and software verification and validation. Results are summarized in the following table.

Table 7.2. Summary of preclinical test results for the Maestro RNR system.

Device Component	Test	Result
Software Validation and Verification	Customized software was developed for the MAESTRO RNR. Test results demonstrated that the software performed according to specifications.	Pass
EMC	Includes analysis of the risks to device performance posed by significant sources of potential electromagnetic interference such as radiofrequency identification (RFID), computed tomography (CT), cellular telephones, and electromagnetic security systems.	Pass
Lead testing	Included simulated implant handling and composite tensile integrity testing; visual inspection testing; visual inspection, electrical isolation, suture wing and suture tab testing; and connector, and flex testing of the lead components	Pass
RNR testing	Includes testing for mechanical load, mechanical shock, vibration, connector retention, connector withdrawal, connector insertion, suture strength and suture fatigue.	Pass

8. CLINICAL STUDIES CONDUCTED PRIOR TO THE RECHARGE PIVOTAL TRIAL

EMPOWER clinical trial

The first clinical study to be conducted in the U.S. was entitled the EMPOWER Clinical Trial for the MAESTRO RF2 System: Vagal Blocking for Obesity Control. The device components include Model 1002 Neuroregulator, Model 2200 Leads, Model 1404 Controller, Model 1403 Transmit Coil and accessories, Model 2500 Programmer Software, and Model P00062-000 Battery Charger. The transmit coil belt was worn "fanny pack" style to optimally align the coil to provide power to the RNR. EMPOWER was designed as a prospective, randomized (2:1), double-blind, controlled trial with evaluation of primary endpoints at 12 months. The intended patient population was those who have a BMI >40 kg/m^2 to 45 kg/m^2, or ≥35 to 39.9 kg/m^2 with obesity related comorbidities. A total of 294 subjects were randomized to either VBLOC (192 subjects) or sham therapy (102 subjects) at 15 institutions. For the sham therapy, the sham patients received the implantable device components as well as lead impedance and safety checks, but the therapy algorithm was set to deliver 0 mA of VBLOC therapy.

The Indications for Use was stated as follows: "The MAESTRO™ Vagal Smart Modulation™ (VSMTM) System is intended for the treatment of obesity."

The transmit coil is used for bi-directional communication between the neuroregulator and controller. The transmit coil is also used to provide power to the neuroregulator via RF that is radiated through the skin. The coil is held in place over the neuroregulator using a coil harness or an elastic strap, or alternatively, with medical tape. The study subjects were required to wear external components that energize the neuroregulator through a radio frequency link.

The first device implantation for the EMPOWER trial was performed in Australia on August 17, 2007. The first US device implantation occurred on September 11, 2007.

EMPOWER Study Results

There were 294 subjects implanted and randomized, including 192 VBLOC (treatment) and 102 sham control subjects. After accounting for subject withdrawals and missed visits, there were 165 VBLOC and 88 sham subjects at the 12 month follow-up. There were a total of 13 serious adverse events (SAEs) in the treatment and control groups of the EMPOWER Study, which were determined to be related to the device, procedure, or therapy at 12 months. The 12 month safety endpoint of serious adverse event rates was met, but the efficacy endpoints were not.

The **primary effectiveness endpoint** was to demonstrate a significantly greater percentage of excess weight loss (% EWL, MetLife method, with a 10% super-superiority margin) with the Maestro System after 12 months of VBLOC Therapy. Results are summarized in Table 8.1 (Table 10-3, page 13, volume 35).

Table 8.1. Mean %EWL in VBLOC and sham control groups.

	Treatment	Control	Difference [95% CI]
N	165	88	
Mean %EWL ± SD	12.1 ± 17.5	12.0 ± 20.8	0.1±18.7
[95% CI]	[9.4, 14.8]	[7.6, 16.4]	[-4.7, 5.0]
P-value*			1.000

*For the hypothesis test with a super-superiority margin of 10%.

Responder rates served **as co-primary effectiveness endpoints**. The stated objective was to demonstrate a significant difference between treatment groups in the proportion of subjects realizing at least a 25% EWL from implant at 12 months post-randomization using the BMI method. Results are summarized in Table 8.2 (Table 10-4, page 14, volume 35).

Table 8.2. Responder rate among EMPOWER subjects receiving VBLOC therapy

Subjects achieving 25% EWL or more (BMI method) at 12 months			
Parameter	**VBLOC**	**Sham**	**Difference (95% CI)**
25% EWL	41 (22.4%)	24 (24.7%)	-2.3 (-14.6, 9.9)

The requirement of patients to wear the transit coil and controller in order for therapy to be delivered with the RF system is believed by EMI to have led to non-compliance of therapy protocols among some study participants. The summary information in Figure 8.1 on device usage versus device effectiveness over the 12 month device implantation period suggests that longer device use was correlated with increased weight loss.

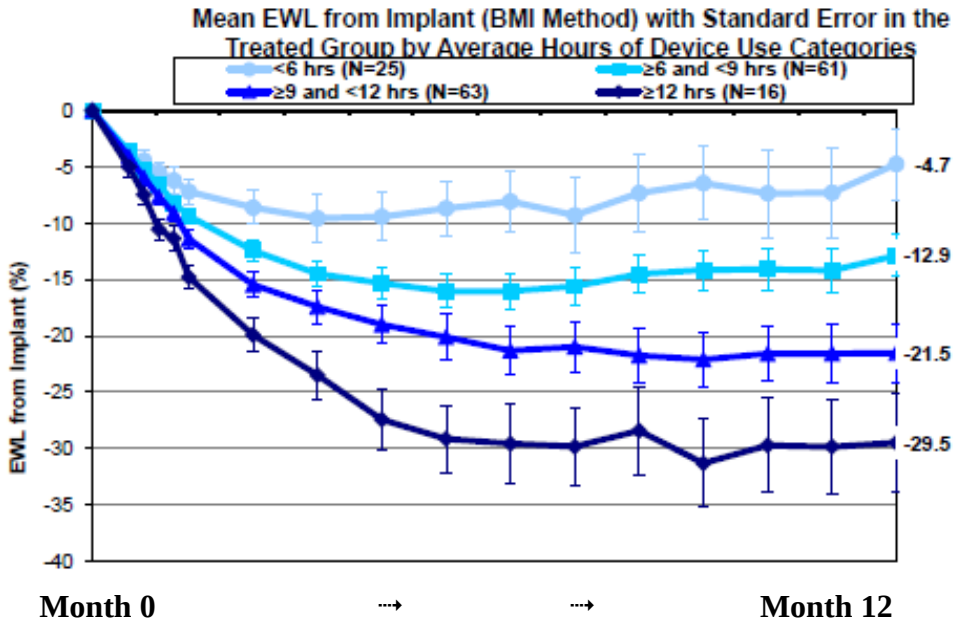

Figure 8.1. Mean %EWL in the VBLOC treated Group by Average Hours of Device Usage (provided by EMI)

The primary safety objective was to estimate the rate of serious adverse events (SAEs) associated with the MAESTRO System and/or implant procedure. For the EMPOWER clinical trial, there were no deaths or unanticipated adverse events (UAEs) observed in the study. Long term safety statistics for the EMPOWER study are provided through May 24, 2013 in the following Tables. Thirty-five (35) AEs occurred within the first 12 months, of which 9 were adjudicated by the Clinical Events Committee (CEC) as being related to either implant/revision procedure or device. Through the 48 month time point, there were 91 SAEs, of which 16 were determined by the CEC as being related to implant/revision procedure, device or therapy. Table 8.3 summarizes the adverse events which occurred within 12 months by severity (Table 10-10, page 19, volume 35). Table 8.4 summarizes the 12 month safety data by severity, and relatedness to device, implant/revision, procedure and therapy (Table 10-9, page 18, volume 35).

Table 8.3. Adverse events observed in the EMPOWER clinical trial through 12 months by investigator-determined severity.

	Treated N=192		Sham N=102	
AE Severity	**N subjects (%)**	**N events**	**N subjects (%)**	**N events**
Mild	166 (86.5%)	613	84 (82.4%)	319
Moderate	129 (67.2%)	358	65 (63.7%)	170
Severe	35 (18.2%)	53	18 (17.6%)	28

Table 8.4. Adverse events observed in the EMPOWER clinical trial through 12 months, by relatedness to implant/revision procedure, device or therapy.

AE Type	Treated N=192		Sham N=102	
	N subjects (%)	N events	N subjects (%)	N events
Adverse events reported, total	180 (93.8%)	1024	94 (92.2%)	517
of which were serious	22 (11.5%)	25	11 (10.8%)	11
AEs related to device, procedure or therapy	148 (77.1%)	424	72 (70.6%)	195
of which were serious	10 (5.2%)	10	3 (2.9%)	3
AEs not related to device, procedure or therapy	156 (81.3%)	600	85 (83.3%)	322
of which were serious	13 (6.8%)	15	8 (7.8%)	8

Some of the AEs which required surgical intervention and/or pain with potential involvement with the implant site are listed below, including instances of the leads twisting, lead detachment, and small bowel obstruction. EMI notes that the length of the leads used with the EMPOWER RF device was 12.5 cm longer than the leads used with the MAESTRO Rechargeable System, and bowel obstruction has not been observed with the shorter leads used in the pivotal ReCharge study (Section 10, below).

- The leads were not implanted parallel to each other, therapy shut down after ramp up (Subject (b) (6)
- Charge that was delivered to the posterior lead was associated with abdominal pain (Subject (b) (6))
- Pulling/tugging feeling in the abdomen/pelvis upon standing/stretching (Subject (b) (6));
- Leads twisted > 20 times, due to the patient's "twiddling" with the neuroregulator (Subject (b) (6) (b)(6))
- Leads were twisted near the neuroregulator, and the RNR had disengaged from the fixation sutures. Patient reported pain (Subject (b)(6))
- The silicone insulation surrounding the antenna was breached, resulting in an exposed coil and impaired communication with external links (Subject (b)(6))
- External devices could not communicate with the RNR (Subject (b)(6)
- High impedance in the posterior lead (Subject (b)(6))
- Short circuit between the posterior tip to posterior ring electrodes. This patient was lost to follow-up (Subject (b)(6)

Additional EMPOWER study safety-related information:

12 Month Safety Data

- 10 (5%) VBLOC subject SAEs related to the device, procedure or therapy

- 4 general surgeries related, 3 implant/revision procedures related and 3 device related
- 11 (6%) VBLOC subjects underwent a surgical intervention
- 5 neuroregulator site pain related, 4 neuroregulator malfunction related, 1 infection related and 1 other

Data as of May of 2013

- 23 (8%) VBLOC subject SAEs related to the device, procedure or therapy
- 7 general surgery related, 6 implant/revision procedure related, 9 device related and 1 therapy algorithm related
- 11 (4%) VBLOC subjects underwent a surgical intervention subsequent to the 1st year
- 5 neuroregulator site pain related, 1 abdominal pain related, 3 device malfunction related and 1 other (headache)
- 1 Sham subject presented 2 years after device placement with severe abdominal bloating and pain. A CT scan demonstrated a small bowel obstruction. An exploratory laparotomy was performed which identified that the small bowel was entangled with the vagal leads (Subject (b)(6))
- Abdominal trauma to the area of the RNR implant site, which caused severe pain (Subject (b)(6) (b)(6))
- Epigastric pain with palpation. Device was explanted (Subject (b)(6))
- Pain at the RNR implant site. The device was explanted (Subject (b)(6)

VBLOC-DM2 Clinical Trial

The VBLOC-DM2 was a pilot study, with a prospective, open-label, multicenter design, to evaluate the MAESTRO RC2 System at 5 sites outside the United States. Twenty eight subjects were enrolled and implanted with the RC2 device. The leads used in this sub-study are 12.5 cm shorter than the leads used with the EMPOWER RF device. All subjects in this trial have Type 2 Diabetes Mellitus. Hours of use with the RC2 device are approximately 14 hours per day. Subjects were monitored for changes in HbA1c and fasting plasma glucose.

- 24.5% EWL (BMI method) was observed in the 26 subjects who completed the 12-month visit.
- One SAE related to device, procedure, or therapy (pain at the neuroregulator site) was observed at 12 months for a rate of 3.6%. Three patients have had device or implant-related SAE through 36 months.
- HbA1c decreased by 1.0 ± 1.1% from a mean 7.8% at baseline.
- Fasting plasma glucose declined 28 ± 42 mg/dl from a mean of 151 mg/dl at baseline.
- Heartburn, constipation and pain at the neuroregulator site were among the most frequently cited AEs.

9. PIVOTAL TRIAL: RECHARGE TRIAL

The primary evidence of safety and effectiveness of the device in support of this PMA comes from the ReCharge Trial, which was approved in March 2011 (under G070025/S49). The ReCharge Trial is a prospective, randomized (2:1), double-blind, sham controlled, multi-center trial to evaluate the safety and effectiveness of the Maestro system in treating obesity. The trial enrolled subjects who had a BMI 40-45 kg/m^2 or a BMI 35-39.9 kg/m^2 with at least one obesity-related co-morbid condition, and who had failed a more conservative weight reduction alternative. Enrollment of subjects with type 2 diabetes was limited to 10% (with no more than 3 such subjects per center). Implanted devices were programmed to deliver approximately 13 hours of therapy per day.

Study Objective

To demonstrate that the MAESTRO RC2 System is safe and effective in providing VBLOC therapy for obese subjects in the target population.

Study Design

Prospective, multicenter, randomized, placebo-controlled study comparing weight loss in participants who received active MAESTRO device therapy (VBLOC group) to weight loss in subjects who received an inactive sham device without lead implants (sham control group).

Subjects and Investigational Sites

A total of 239 subjects were enrolled at 10 investigational sites (8 in the US, 2 in Australia). This total included 162 randomized to the device group, and 77 randomized to the sham control group. Subjects

randomized to the sham control underwent a surgical procedure consisting of anesthesia, implantation of a non-functional neuroregulator, and the same number of incisions an investigator would use during the laparoscopic placement of the leads.

Randomization Scheme

At the time of implant, eligible, non-diabetic subjects were randomized (2:1) to either the VBLOC group or the sham group, with the randomization stratified by investigational site, using randomly varying block sizes of 3 and 6. The same randomly varying block sizes were used for diabetic subjects, but without stratification by site. The enrollment of diabetic subjects was limited to 10% those enrolled.

Enrollment

The active MAESTRO RC2 System was implanted in 157 subjects, while 76 subjects were implanted with the sham device. The sham group was implanted with the RNR at the same location as the functional device, but without undergoing the procedure of attaching the electrodes to the vagus nerve branches. A sham surgical procedure consisted of the same number of incisions (approximately 5) that the investigator place using general laparoscopic techniques. The battery in the sham device becomes depleted and interacts with the programmer in the same fashion as the active device. All subjects remained blinded through at least the 12 month follow-up visit, after which the sham subjects who chose to continue in the trial had the option of having the MAESTRO Rechargeable System fully implanted, and receiving active therapy.

All subjects participated in a weight management program, consisting of recommendations regarding diet, exercise, and behavior modification throughout the study. The ReCharge behavioral weight loss program is similar to the program used in the EMPOWER study (Section 10.1, Volume 22). All subjects were taught the same basic information about weight loss and physical activity, and were given the opportunity to practice related behavioral skills both during educational sessions and at home. Modifications to their current diet and exercise plan were taught by a trained adviser through seventeen individual sessions during the first year along with the regularly scheduled trial visits. The subjects were required to complete a 7 day diet and exercise diary prior to the implant, weeks one through four, and once per month during the first year of the study. Following the first year, group sessions were scheduled for the duration of the study. Subjects were required to cover the elements of the curriculum in a minimum 17 individual face-to-face sessions during the first 12 months after initiation in order to complete the year one behavioral weight loss instruction.

Select Inclusion Criteria:

1. Informed consent
2. Men or Women
3. 25-65 years of age inclusive
4. BMI between 40 kg/m2 and 45 kg/m2, or a BMI between 35 kg/m2 and 39.9 kg/m2 with at least one obesity related co-morbid condition. Co-morbid conditions may include one or more of the following:
    - Type 2 diabetes mellitus (limited to 10% of randomized subjects)
    - Hypertension as defined by systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90
        i. mmHg
5. Treated or untreated with systolic ≥ 140 mmHg and/or diastolic ≥90 mmHg
6. Treated with systolic < 140 mmHg and/or diastolic < 90 mmHg
    - Dyslipidemia as defined by total cholesterol ≥ 200 or LDL ≥ 130
7. Treated or untreated with total cholesterol ≥ 200 or LDL ≥ 130
8. Treated with total cholesterol < 200 or LDL < 130
    - Sleep apnea syndrome (confirmed by overnight p02 studies)
    - Obesity-related cardiomyopathy
9. Type 2 diabetes mellitus subjects with:
    - Glycosylated hemoglobin (HbA1c) 7.0-10 % inclusive at screening visit (Undiagnosed subjects that are found to have a HbA1c 7-10% at screening must see their primary physician for diagnosis and medical treatment before continuing in trial)
    - Onset: 12 years or less since initial diagnosis
    - Currently not using insulin therapy, GLP-1 receptor agonists (e.g., exenatide), for diabetes treatment and have not been on these treatments in the past 6 months.
    - Creatinine within normal reference range
    - No history of proliferative retinopathy
    - No history peripheral neuropathy
    - No history of autonomic neuropathy
    - No history of coronary artery disease, with or without angina pectoris
    - No history of peripheral vascular disease
10. Failure to respond to a supervised diet/exercise programs in which the subject was engaged within the last five years.
11. Ability to complete all study visits and procedures.

Select Exclusion Criteria:

1. History of Crohn's disease and/or ulcerative colitis
2. History of bariatric surgery, fundoplication, gastric resection or major upper-abdominal surgery (acceptable surgeries include cholecystectomy, hysterectomy),
3. Clinically significant hiatal hernias (> 5cm) known from subject's medical record or determined by barium swallow (upper GI x-ray) or upper endoscopy per PI discretion prior to implant
4. Current cirrhosis, portal hypertension and/or esophageal varices
5. Intra-operative exclusion: hiatal hernia requiring surgical repair or extensive dissection at esophagogastric junction at time of surgery
6. Treatment with prescription weight-loss drug therapy within the prior three months and the use of prescription drug therapy or the use of over-the-counter weight loss preparations for the duration of the trial
7. Known genetic cause of obesity (e.g., Prader-Willi Syndrome)
8. Weight loss of more than 10% of body weight in the previous 12 months
9. Physician-prescribed pre-operative weight loss program prior to surgery. Note: Study subject may continue any personal eating plan they were on prior to study enrollment (see exclusion criterion #24)
10. Current type 1 diabetes mellitus (DM)
11. Current alterations in treatment for thyroid disorders (stable treatment regimen for prior three months acceptable)
12. Current treatment for peptic ulcer disease (previous history acceptable)
13. Chronic treatment (more than 4 weeks of daily use) with narcotic analgesic drug regimens (treatment with non-steroidal anti-inflammatory drugs acceptable)

14. Current alterations in treatment regimens of anti-cholinergic drugs, including tricyclic antidepressants (stable treatment regimen for prior six months acceptable)
15. Current medical condition that, in the opinion of the investigator, would make subject unfit for surgery under general anesthesia or that would be exacerbated by intentional weight loss. Some examples include diagnosis of cancer, recent heart attack, recent stroke, or recent serious trauma
16. Presence of permanently implanted electrical powered medical device or implanted gastrointestinal device or prosthesis (e.g., pacemakers, implanted defibrillators, neurostimulators etc.)
17. Planned or contemplated use of magnetic resonance imaging (MRI) or oncologic radiation during the course of the trial
18. Psychiatric disorders (including untreated severe depression, schizophrenia, substance abuse, bulimia nervosa, etc.) or limited intellectual functioning which would potentially compromise the participant's ability to fully comprehend and/or cooperate with the study protocol. Psychiatric disorders will be established by a review of subject's medical history. For depression,a BDI score $\geq$ 29 will be considered to indicate severe depression
19. Current, active member of an organized weight loss program (e.g., Weight Watchers, TOPS)
20. Current participant in another weight loss study or other clinical trials
21. Patient reported:
    - Inability to walk for about 10 minutes without stopping
    - Feeling of pain in chest when doing physical activity
    - Feeling of pain in chest when not doing physical activity

Patient Monitoring and ReCharge Therapy

Tables 9.1 and 9.2 summarize the scheduled visits and patient assessments.

Table 9.1. Schedule of trial events: Screening through 12 month follow-up (Table 3.1, page 14, appendix G, volume 35)

Screening [Enrollment]	Randomization/ Implant/ Initiation	Week 1 Visit 7 ±3 days after Implant	Follow-up Visits 2, 3, 4, 6, 8, 10, 12 weeks (±3 days) 4, 5, 6, 7, 8, 9, 10, 11, 12 months (±14 days) after randomization
• Informed consent • Inclusion/exclusion criteria assessments • Body weight • Body height • Vital signs* • Medication use assessment • Psychological assessment • Waist and hip circumferences • Clinical laboratory assessments • Subject Questionnaires • Physical exam • 7 day diet and activity diary • 12 lead ECG • Preoperative assessments (upper GI xray or upper endoscopy) • Device overview and training	• Body weight • Vital signs • Adverse event/medication use assessment • Randomized to treatment groups • Device implant (after all procedures above)	• Subject self-assessment (optional) • Body weight • Vital signs • Adverse event / medication use assessment • Device training • 7 day diet and activity diary • Blinding status • Weight management begins	• Subject self-assessment (optional) • Body weight • Vital signs* • Adverse event/medication use assessment • Physical exam if needed • Clinical laboratory assessments (6 &12 months) • Waist and hip circumferences (12 months) • Weight management • Device interrogation • Current amplitude adjustments as indicated • Assess/maximize compliance with recharging • 12 lead ECG (4, 8, 12 months) • 7 day diet and activity diary • Blinding status (6 & 12 mo) • Subject Questionnaires (3, 6 & 12 mo) • Telephone contact with subject between visits (12 week- 6 months)

* Blood pressure collected in triplicate at screening, implant, months 3, 6, 9, and 12 month visits.

Table 9.2. Schedule of trial events: 12 months through 60 months follow-up

Follow-up Visits **13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60 months (±14 days) after randomization[#]**
• Subject self-assessment (optional) • Body weight • Vital signs* • Adverse event/medication use assessment • Clinical laboratory assessments (24, 36, 48 and 60 months) • Waist and hip circumferences (24, 36, 48, and 60 months) • Weight management (Individual at all visits and group quarterly) • Device interrogation • Current amplitude adjustments as indicated • Assess/maximize compliance with recharging • Subject Questionnaires (18, 24, 30, 36, 42, 48, 54, and 60 months)

* Blood pressure collected in triplicate at 18, 24, 30, 36, 42, 48, 54, and 60 months visits.

[#] Once control group subjects receive a fully functioning device, they will be seen according to the year one follow-up schedule for the next 12 months

The VBLOC treatment group neuroregulators were initially set to deliver an amplitude of 1 mA with a treatment schedule of 13 hours per day. The amplitude was increased to 3 mA at the week 1 visit, and increased by 1 mA each following week reaching 6 mA at week 4. The programming sessions and the systematic amplitude increases were performed for both VBLOC and sham groups to maintain blinding. Subjects who could not tolerate 3 mA at week 1, or 1 mA incremental increases, were increased at a slower rate and/or smaller increments. Other therapy parameters included a ramp-up time of 0 to 50 seconds, an ON time of 2 to 5 minutes and an OFF time of 5 to10 minutes. Therapy at 6 mA (or the maximal tolerated amplitude) and a 13 hour delivery schedule per day were then maintained for the remainder of the first 6 months. At month 6 the goal was for subjects to achieve a 15% EWL. Any subjects reporting unacceptable adverse events that were possibly related to therapy underwent modifications of the device parameters including a decrease in amplitude, an increase in the off Time, an increase or decrease ramp-up time or an adjustment in the daily treatment schedule.

Beyond the six month visit, the therapy settings were left unchanged if the subject was losing weight and was not experiencing unacceptable adverse events. At the 6, 7, 8, 9, 10, and 11 month visits, the subjects had their % EWL from implant compared with the expected rate of 2.5% EWL per month. If the subject was either not losing weight at an expected rate or was experiencing unacceptable adverse events, the therapy settings were adjusted up or down. If a subject lost more than 2.5% EWL, no changes were

made in the settings. Subjects that achieved the monthly %EWL but gained weight from the previous month had further adjustments in the therapy parameters. The maximum amplitude setting was 8.0 mA, and the maximum daily hours of VBLOC therapy was 18 hours.

Overall, there were no differences at 12 months in the neuroregulator amplitude settings (VBLOC group mean of 5.7 mA; sham group mean of 6.1 mA) or the hours of therapy received per day (VBLOC group mean of 12.2 hours; sham group mean of 12.0 hours) between the groups. The therapy settings for all subjects were adjusted by a blinded coordinator.

Endpoints and statistical analysis

This section provides an overview of the definitions and hypotheses for the pre-specified endpoints that were evaluated in the ReCharge Trial. A comprehensive summary of the results for each of these endpoints is given in Section 10.

Primary effectiveness endpoints %EWL (BMI method)

There were two co-primary effectiveness endpoints.

The first co-primary effectiveness endpoint was percent excess weight loss (%EWL) at 12 months after randomization, with ideal body weight calculated using the BMI method (i.e., the weight a subject would have with a BMI of 25 kg/m^2). The goal of the analysis of this co-primary endpoint was to show that the mean %EWL in the VBLOC group is at least 10% greater than the %EWL in the sham group (i.e., there was a pre-specified super-superiority margin of 10%). The null and alternative hypotheses can be stated as

$$\text{Ho: } \mu_T \leq \mu_C + 10\% \quad \text{vs.} \quad \text{Ha: } \mu_T > \mu_C + 10\%,$$

where μ_T (μ_C) is the mean %EWL in the VBLOC treatment (sham control) group. The test was carried out using a t-test with a significance level of 0.025.

The second co-primary effectiveness endpoint was based on two definitions of subject-level response depending on level of %EWL (using the BMI method):

- Observe at least 55% of VBLOC subjects with at least 20% EWL at 12 months.
- Observe at least 45% of VBLOC subjects with at least 25% EWL at 12 months.

The evaluation of this co-primary endpoint was based on observed proportions only rather than statistical hypothesis tests.

Secondary effectiveness endpoint: %EWL (Met Life method)
The secondary effectiveness endpoint was %EWL at 12 months after randomization, with ideal body weight determined using the Met Life tables (i.e., using the upper limit of the specified weight range, given a subject's gender and height). As with the primary endpoint, the goal was to show that the treatment group %EWL is at least 10% greater than the %EWL in the sham group. As with the primary endpoint, the null and alternative hypotheses are

Ho: $\mu_T \leq \mu_C + 10\%$ vs. Ha: $\mu_T > \mu_C + 10\%$,

where μ_T (μ_C) is the mean %EWL in the VBLOC treatment (sham control) group. The test was carried out using a t-test with a significance level of 0.025.

Additional supportive effectiveness assessments
Additional pre-specified effectiveness endpoints included percentage of total body weight loss (%TBL), Impact of Weight on Quality of Life (IWQOL-Lite), Three Factor Eating Questionnaire (TFEQ), and Beck Depression Inventory (BDI-II).

Primary safety endpoint
The primary safety endpoint is the rate of serious adverse events (SAEs) related to implant or revision procedures, device, or therapy in the VBLOC group through 12 months of follow-up. The goal of the analysis was to show that this SAE rate is less than a pre-specified performance goal of 15%. The null and alternative hypotheses for this endpoint can be stated as

Ho: $\pi_T \geq 15\%$ vs. Ha: $\pi_T < 15\%$,

where π_T is the SAE rate in the VBLOC treatment group at 12 months, as described above.

10. RECHARGE STUDY RESULTS

This section contains a description of the results from the ReCharge trial. Briefly, the trial did not meet the pre-specified co-primary effectiveness endpoints, but did meet the pre-specified primary safety endpoint.

The first co-primary effectiveness endpoint specified that the device would achieve a mean percent excess weight loss (%EWL) that is at least 10% greater than the sham control mean %EWL. The average %EWL at 12 months was 24.4% (SD=23.6%) in the VBLOC group and 15.9% (SD=17.7%) in the sham group, resulting in an average difference between the VBLOC and sham groups of 8.5% (95% CI: [3.1%, 13.9%]). While these results would support a conclusion that average %EWL is higher in the VBLOC group than in the sham group, the pre-specified superiority margin of 10% was not achieved, because the lower bound of the confidence interval is less than 10%.

The second co-primary effectiveness endpoint had two requirements: (i) at least 55% of VBLOC subjects would achieve a %EWL of at least 20%; and (ii) at least 45% of VBLOC subjects would achieve a %EWL of at least 25%. The assessments of these objectives were based on observed rates rather than statistical hypothesis tests, and according to the protocol both of these objectives should be met for trial success. Based on the results of this trial, neither of the co-primary objectives was met: (i) 52.5% (<55%) of VBLOC subjects had a %EWL of at least 20%; (ii) 38.3% (<45%) of VBLOC subjects had a %EWL of at least 25%.

The secondary effectiveness endpoint was similar to the first co-primary effectiveness endpoint, i.e., to show that %EWL with VBLOC therapy is at least 10% greater than with the sham control, with the exception that ideal body weight was determined by the Met Life method (assuming a medium frame and given a subject's height and gender, the ideal body weight is the upper limit of the weight range specified in the Met Life tables). The results were similar to those obtained for the primary %EWL endpoint. The average %EWL at 12 months was 22.2% (SD=21.4%) in the VBLOC group and 14.4% (SD=15.9%) in the sham group, so that the average difference between the VBLOC and sham groups was 7.8% (95% CI: [3.0%, 12.7%]). Again, the pre-specified superiority margin of 10% was not achieved.

The primary safety endpoint of the ReCharge trial was to demonstrate that the 12-month serious adverse event (SAE) rate related to implant or revision procedures, device, or therapy was less than a performance goal of 15% among the subjects in the VBLOC group. There were 6 SAEs identified in these categories, which led to an observed SAE rate of 3.7% (6/162, 95% CI: [1.4%, 7.9%]) among the VBLOC subjects, which met the primary safety endpoint, because the upper bound of this confidence interval is less than 15%.

As discussed in Section 11, there were also 9 subjects who had SAEs related to the general surgical procedure. When these SAEs were counted as part of the primary safety endpoint, using an intent-to-treat analysis, the SAE rate was 8.6% (14/162), with a 95% CI of [4.8%, 14.1%], which also meets the performance goal of 15%.

Subject Demographics and Baseline Evaluations

The trial included 239 randomized subjects (162 VBLOC and 77 sham) at 10 investigational sites (8 in the US and 2 in Australia). Of the 239 randomized subjects, 233 received an implanted device (157 VBLOC, 76 sham). Among the randomized subjects, 84.9% of the subjects were female, 92.9% were Caucasian, the average age was 47 years (range: 18-65), average BMI at implant was 40.9 kg/m^2 (range: 34.4-48.4), and 5.4% had type 2 diabetes mellitus. No significant differences were found between the VBLOC and sham groups for any of the recorded demographic and baseline variables. Table 10.1 (excerpted from Table 9-26, page 66, volume 22) summarizes the demographics and baseline characteristics of the study participants.

Table 10.1. Baseline Demographics and Health Characteristics of Recharge Subjects

Characteristic		VBLOC (N=162)	Sham (N=77)	Overall (N=239)	P-value
Gender	Female	87.0%	80.5%	84.9%	0.245
	Male	13.0%	19.5%	15.1%	
Age (years)		47.1±10.3 (18.7, 65.9)	46.6±9.4 (24.8, 64.1)	47.0±10.0 (18.7, 65.9)	0.693*
Ethnicity	Hispanic/ Latino	3.7%	7.8%	5.0%	0.209
Race	Caucasian	92.0%	94.8%	92.9%	0.592
	African American	4.9%	3.9%	4.6%	1.000
	Other	3.1%	1.3%	2.5%	0.667
Height (m)		1.7±0.1 (1.5, 1.9)	1.7±0.1 (1.5, 2.0)	1.7±0.1 (1.5, 2.0)	0.112*
BMI (implant)		40.9±2.8 (34.4, 46.4)	40.9±3.1 (35.2, 48.4)	40.9±2.9 (34.4, 48.4)	0.969*
Weight at implant (kg)		112.6±13.4 (79.4, 158.8)	115.5±14.3 (89.4, 160.2)	113.5±13.7 (79.4, 160.2)	0.117

NOTE: Data are presented as percentages or mean ± SD (min, max). P-values for continuous variables are based on two-sample t-test or Wilcoxon rank-sum test (*). P-values for categorical variables are based on Fisher's exact test.

<u>Panel Question</u>: The panel will be asked to discuss the generalizability of the study results, based on the study population.

Table 10.2 provides an enrollment summary by investigational site. The first two sites (Adelaide Bariatric Centre and Institute for Weight Control) are located in Australia, and the other eight sites are located in the US.

Table 10.2. Summary of the number of subjects randomized and implanted by investigational site.

Center	Screened	Randomized	Implanted	N Randomized	
				VBLOC	Sham
Adelaide Bariatric Centre	37	28	27	19	9
Institute of Weight Control	41	29	29	21	8
Mayo Clinic Rochester	24	14	14	9	5
Oregon Health & Science Univ.	34	25	25	17	8
Scottsdale Bariatric Center	50	29	29	20	9
Scripps Clinic	43	26	24	18	8
Stanford University School of Medicine	8	5	5	3	2
Tufts Medical Center	44	26	25	16	10
University of Minnesota	91	33	33	23	10
Virginia Commonwealth Univ.	48	24	22	16	8
TOTAL	420	239	233	162	77

Subject accounting and follow-up

Enrollment in the ReCharge trial began on May 16, 2011, and was completed on December 27, 2011. Figure 10.1 provides a summary of the numbers of subjects randomized, implanted, and remaining in the study through 12 months of follow-up (when the primary safety and effectiveness endpoints were evaluated). Note that six randomized subjects (5 VBLOC and 1 sham) were not actually implanted. The subject in the sham group changed his mind just prior to surgery. Of the five non-implanted subjects randomized to the VBLOC group, three were not implanted due to intra-operative exclusions, one was due to a comorbid condition, and one was due to discretion of the implanting physician. The overall follow-up rate through 12 months was 89.1% (213/239), with follow-up rates of 90.7% (147/162) in the VBLOC group and 85.7% (66/77) in the sham group. Follow-up through the month 18 visit is summarized in Table 10.3.

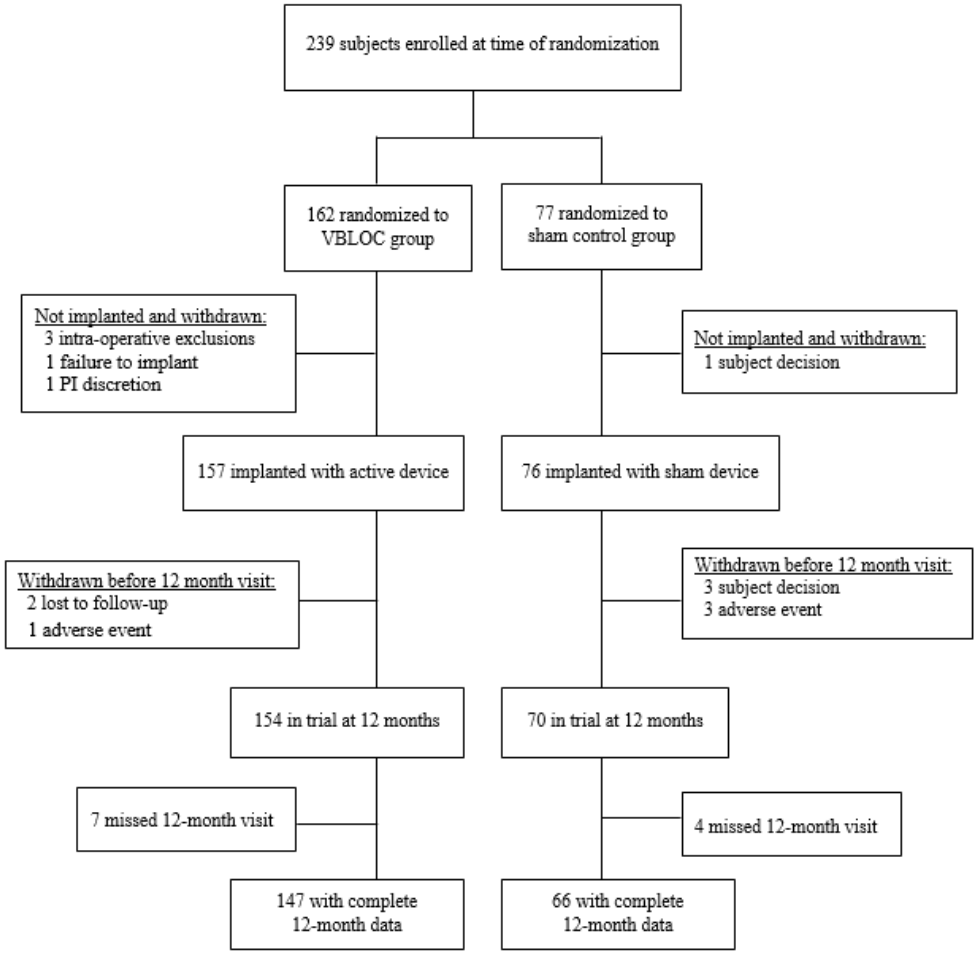

Figure 10.1. Summary of subject follow-up from randomization through month 12

Table 10.3. Subject accounting of the intent-to-treat population through the month 18 follow-up visit (copied from Table 1-1: Subject Disposition Through 18-Month Visit, page 8, volume 1, Amendment 3)

Study Period	VBLOC	Sham	Overall
Randomized	**100.0% (162)**	**100.0% (77)**	**100.0% (239)**
Not implanted and withdrawn before 12 month visit	3.1% (5)	1.3% (1)	**2.5% (6)**
Implanted	**96.9% (157)**	**98.7% (76)**	**97.5% (233)**
Implanted & withdrawn before 12 month visit	1.9% (3)	7.8% (6)	3.8% (9)
Total in the trial at 12 months	**95.1% (154)**	**90.9% (70)**	**93.7% (224)**
Completed 12 month visit	90.7% (147)	85.7% (66)	**89.1% (213)**
Did not complete 12 month visit	4.3% (7)	5.2% (4)	**4.6% (11)**
Total in the trial at 18 months	**87.7% (142)**	**83.1% (64)**	**86.2% (206)**
Completed 18 month visit	72.2% (117)	54.5% (42)	**66.5% (159)**
Did not complete 18 month visit	**15.4% (25)**	**28.6% (22)**	**19.7% (47)**

Before proceeding to the detailed results for the pre-specified primary and secondary effectiveness endpoints, it is informative to look at the subject weights at baseline and at each of the follow-up visits. Figure 10.2 shows the average weights with standard deviations for the VBLOC and sham groups through 12 months. Table 10.4 provides summary statistics for the subject weights over the course of the trial. Based on the weights available at both baseline and month 12, the mean change in weight from baseline to 12 months was 24.5 lbs (N=147, SD=22.5) in the VBLOC (treatment) group and 16.8 lbs (N=66, SD=17.9) in the sham (control) group, resulting in a mean difference between the VBLOC groups of 7.7 lbs (95% CI: [2.0, 13.4]).

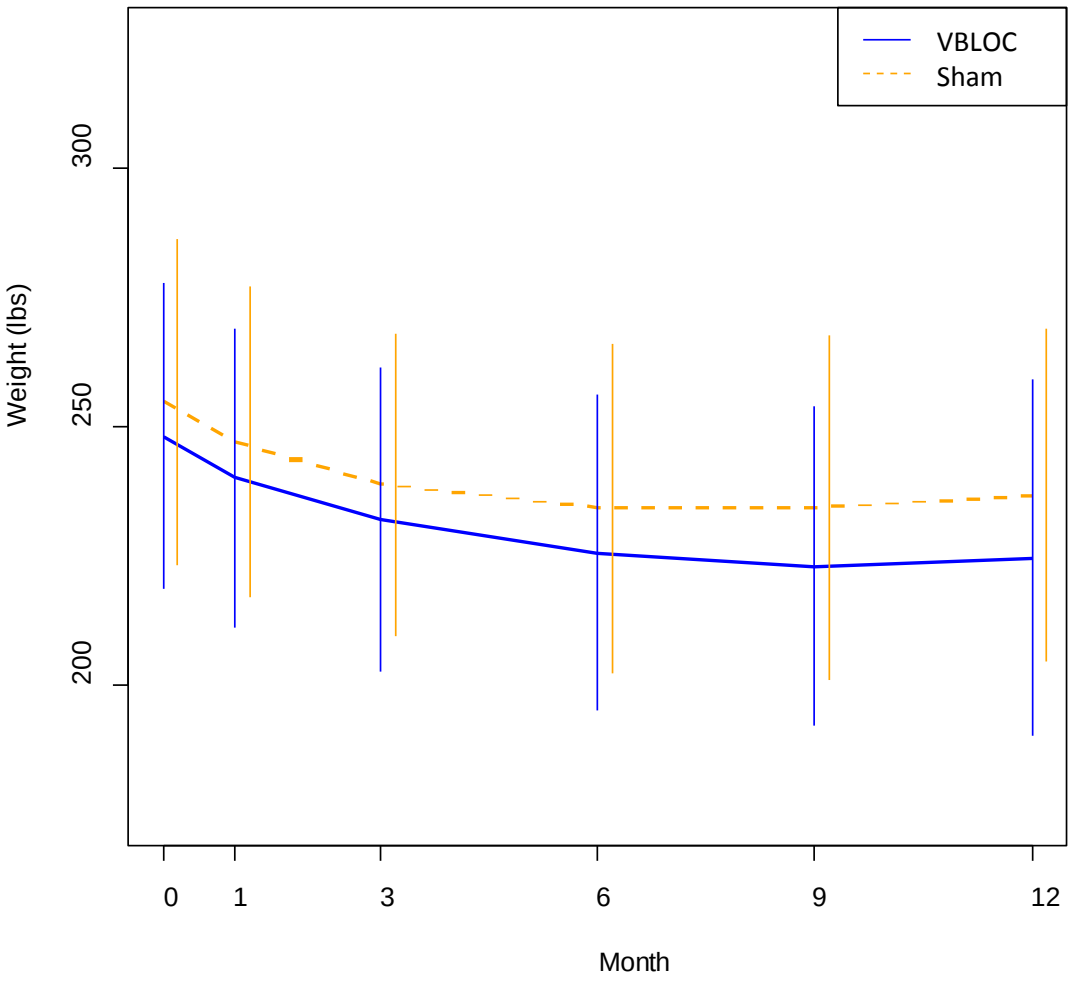

Figure 10.2. Average weights (lbs) +/- standard deviations by treatment group through 12 months of follow-up.

Table 10.4. Summary of weights (lbs) by treatment group through 12 months of follow-up.

Visit month	Treatment group	N	Mean (lbs)	Std Dev (lbs)	Min (lbs)	Max (lbs)
0	VBLOC	162	248.1	29.6	175.0	350.0
	Sham	77	254.7	31.5	197.1	353.2
1	VBLOC	152	240.0	28.9	169.8	334.0
	Sham	75	247.0	30.2	193.0	345.2
3	VBLOC	151	232.0	29.3	160.9	317.0
	Sham	71	238.7	29.3	187.0	306.5
6	VBLOC	149	225.5	30.5	160.5	317.0
	Sham	69	234.2	31.9	169.5	315.7
9	VBLOC	135	223.0	31.0	153.9	314.5
	Sham	60	234.3	33.3	155.0	312.2
12	VBLOC	147	224.6	34.5	144.6	331.0
	Sham	66	236.6	32.3	153.4	309.0

Figure 10.3 displays the observed weights at implant (month 0) and months 1, 3, 6, 9, and 12. The left panel shows the weights for subjects in the VBLOC group, while the right panel shows the weights for subjects in the sham group. VBLOC means are shown over the individual subject weights for each treatment group.

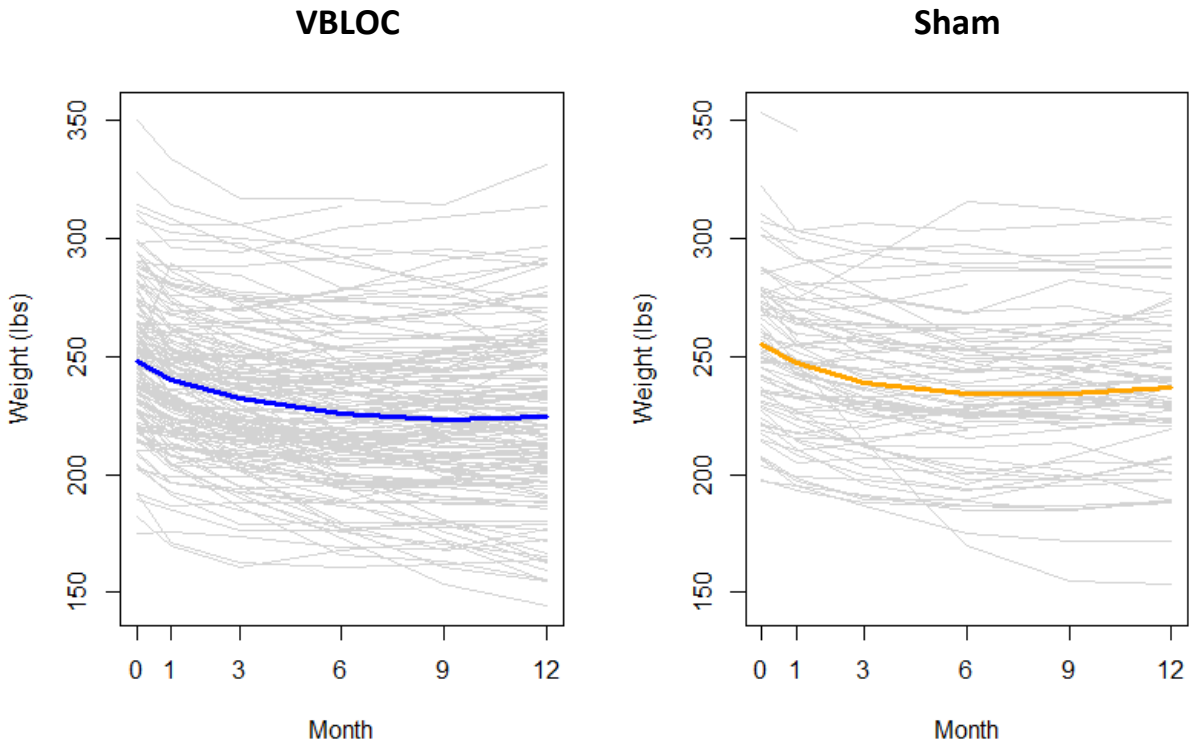

Figure 10.3. Average weights (lbs) for the VBLOC (left panel) and sham (right panel) groups, superimposed over all available subject weights at months 0, 1, 3, 6, 9, and 12.

First co-primary effectiveness endpoint results:

The first co-primary effectiveness endpoint was percent excess weight loss (%EWL) at 12 months after randomization, with ideal body weight calculated using the BMI method (i.e., the weight a subject would have if their BMI was 25 kg/m^2). The null and alternative hypotheses can be stated as

$$\text{Ho: } \mu_T \leq \mu_C + 10\% \quad \text{vs.} \quad \text{Ha: } \mu_T > \mu_C + 10\%,$$

Where μ_T (μ_C) is the mean %EWL in the VBLOC treatment (sham control) group, so that the goal of the analysis of the primary endpoint was to show that the mean %EWL in the VBLOC group is at least 10% greater than the %EWL in the sham group. Table 10.5 summarizes the results for this endpoint. Based on these results, the device did not perform 10% better than sham with respect to %EWL, since the confidence interval of [3.0, 14.8] has a lower bound that is less than 10%.

Table 10.5. Results of the analysis for the first co-primary effectiveness endpoint (%EWL based on the BMI method) in the ITT group. (NOTE: The mean, min, max and 95% CI values are all %EWL.)

Excess Weight Loss (%) (BMI Method)	VBLOC	Sham	Difference
N	162	77	
Mean ± SD	24.4 ± 23.6	15.9 ± 17.7	8.5 ± 21.9
(Min, Max)	(-20.6, 102.7)	(-30.7, 103.7)	
[95% CI]	[20.8, 28.1]	[11.9, 19.9]	[3.1, 13.9]
P-value (Delta = 10%)			0.708

Remark: The failure of the analysis of this primary endpoint to meet the super-superiority margin of 10% may be partially explained by the higher than expected %EWL of 15.9% observed in the sham group. When planning the trial, EMI based the sample size calculations on an expected treatment effect of 20%. However, the study showed a VBLOC effect of only 8.5%.

Remark: As shown earlier, the VBLOC groups were fairly balanced with respect to the measured demographics and baseline characteristics. Because of this balance, the EMI did not consider any regression models assessing the effect of baseline variables on %EWL. However, FDA has examined the effect of VBLOC on %EWL using linear regression models with various combinations of the following candidate covariates: implant BMI, race, sex, age, and OUS (an indicator of whether a site is outside the US). FDA has found that the regression models considered produce inferences about the treatment effect that are consistent with the unadjusted analyses presented elsewhere in this executive summary. As an example, one model considered included implant BMI, age, and treatment. This model produced an estimated treatment effect of 8.46% (standard error 2.97), giving an approximate 95% CI of [2.64%, 14.28%].

An additional analysis of the first co-primary endpoint and the hypothesis test stated above was carried out in the per-protocol (PP) group, which was defined as all ITT subjects except those who (i) were not implanted, (ii) did not have therapy initiated within 45 days of implant, (iii) had therapy discontinued due a long-term (>2 months) medical condition, or (iv) had a missing weight at 12 months. The results in the PP group were similar to those for the ITT group, as shown the following table.

Table 10.6. Results of the analysis for the first co-primary effectiveness endpoint (%EWL based

on the BMI method) in the PP group. (NOTE: The mean, min, max and 95% CI values are all %EWL.)

Excess Weight Loss (%) (BMI Method)	Treatment	Control	Difference
N	146	65	
Mean ± SD	26.3 ± 23.8	17.3 ± 18.1	8.9 ± 22.2
(Min, Max)	(-13.9, 102.7)	(-30.7, 103.7)	
[95% CI]	[22.4, 30.2]	[12.9, 21.8]	[3.0, 14.8]
P-value (Delta = 10%)			0.640

Figure 10.4 provides a graphical summary of the %EWL in the VBLOC and sham control groups through 12 months of follow-up.

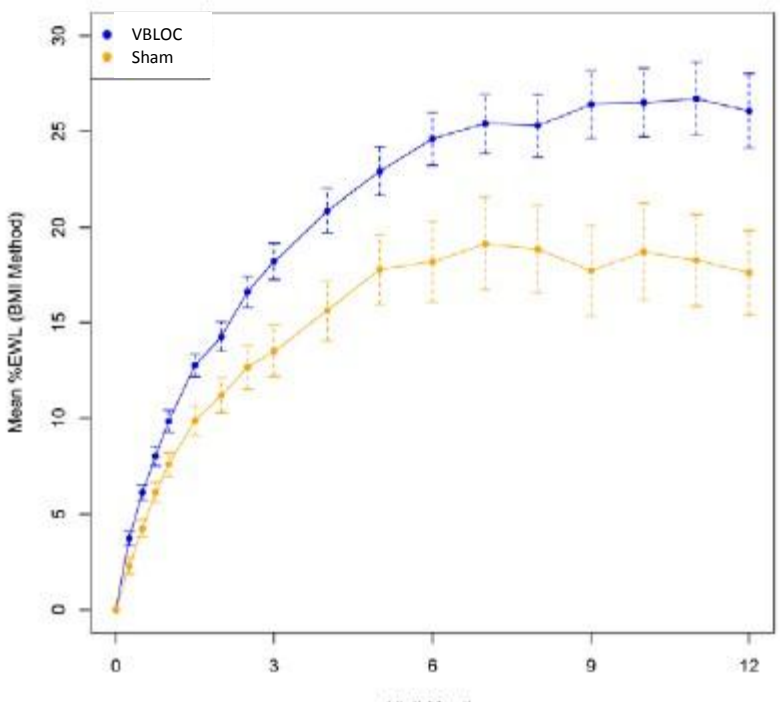

Figure 10.4. Percent excess weight loss (%EWL) +/- standard error through 12 months for each treatment group (in the per protocol (PP) group, i.e., without imputation of any missing values).

Sensitivity analyses: impact of missing data

As noted above, 15 subjects in the VBLOC group (9.3%) and 11 subjects in the sham group (14.3%) did not complete 12 months of follow-up. The impact that these missing weights had on the results for the first co-primary endpoint was investigated through two approaches.

- Longitudinal mixed-effects regression model of the available %EWL data. The estimated difference in %EWL between the VBLOC and sham groups was 9.7% (95% CI: [6.1%, 13.2%]).

- A multiple imputation model which included assigned treatment, site, gender, age, race, weight at screening and diabetes status. 50 "completed" datasets were formed from the multiple imputations and analyzed. The combined results provided an estimated difference in %EWL between treatment groups of 8.8% (95% CI: [2.8%, 14.8%]).

The results of these sensitivity analyses are consistent with the results obtained from the ITT analysis (that used LVCF to impute any missing 12-month weights) and the PP analysis (which is essentially based on subjects with both baseline and 12-month weights). All analyses result in the conclusion that there is no evidence to support the super-superiority hypothesis.

Further analysis of the first co-primary effectiveness endpoint in the ITT group is provided in Table 10.7, below. In this analysis, the treatment comparisons are given by investigational site. EMI fit a linear regression model of %EWL that included a treatment-by-site interaction term, but this interaction was not significant (p-value=0.72).

Table 10.7. Summary of treatment comparisons in the ITT group by investigational site. (NOTE: All mean, SD and 95% CI values are %EWL.)

Site	VBLOC Mean ± SD (N)	Sham Mean ± SD (N)	Difference Mean ± SD [95% CI]
Adelaide Bariatric Centre	44.9 ± 28.2 (19)	35.1 ± 29.4 (9)	9.9 ± 28.6 [-15.1, 34.9]
Institute of Weight Control	28.4 ± 22.7 (21)	13.7 ± 21.7 (8)	14.7 ± 22.4 [-5.0, 34.4]
Mayo Clinic Rochester	20.6 ± 14.1 (9)	25.0 ± 14.6 (5)	-4.4 ± 14.3 [-23.0, 14.1]
Oregon Health & Science University	16.0 ± 21.1 (17)	11.1 ± 16.0 (8)	4.9 ± 19.7 [-11.1, 21.0]
Scottsdale Bariatric Center	18.3 ± 22.1 (20)	6.9 ± 7.7 (9)	11.3 ± 19.0 [-0.1, 22.8]
Scripps Clinic	22.9 ± 21.0 (18)	6.4 ± 12.7 (8)	16.5 ± 18.9 [2.6, 30.3]
Stanford University School of Medicine	16.9 ± 16.0 (3)	16.2 ± 3.2 (2)	0.8 ± 13.2 [-36.4, 37.9]
Tufts Medical Center	26.3 ± 26.8 (16)	10.8 ± 14.2 (10)	15.5 ± 22.9 [-1.2, 32.2]
University of Minnesota	22.7 ± 17.1 (23)	15.6 ± 6.9 (10)	7.0 ± 14.9 [-1.5, 15.6]
Virginia Commonwealth University	17.3 ± 26.2 (16)	22.1 ± 12.2 (8)	-4.7 ± 22.7 [-21.0, 11.5]

<u>Panel Question</u>: The panel will be asked to discuss whether the first co-primary endpoint results support the effectiveness of the device.

Weight loss through month 18 follow-up

Figure 10.5 shows the %EWL by treatment group through the18 month follow-up visit. The assessment of the treatment effect at month 18 is complicated by the following:

- Incomplete follow-up, with follow-up rates of 72.2% and 54.5% in the VBLOC and sham groups, respectively.
- The blind was broken in the sham group after all subjects completed the 12-month visit. Most subjects were unblinded at the 16 month visit or after.

At 18 months, the observed mean %EWL in the VBLOC group was 25.2% (95% CI: [20.6, 29.8]) and 11.7% (95% CI: [5.4, 18.0]) in the sham control group, resulting in a treatment difference of 13.5% (95% CI: [5.7, 21.3]). Analysis of the 18-month data from the ReCharge study suggests maintenance of the weight loss seen at 12 months.

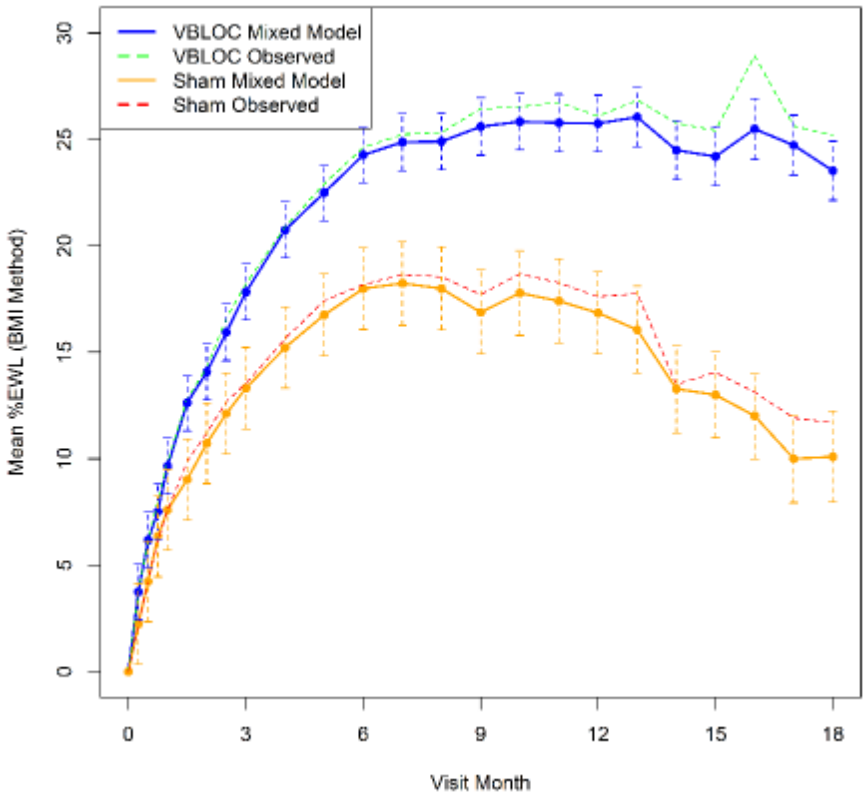

Figure 10.5. Summary of %EWL by treatment group through the month 18 follow-up visit (from Figure 1-1: Mean % EWL ± Standard Error from Mixed Effects Regression Model and % EWL as Observed.

Panel Question: The panel will be asked to discuss whether the 18 month %EWL data support the effectiveness of the device.

Second co-primary effectiveness endpoints: %EWL responder rates

As discussed earlier, the second co-primary effectiveness endpoint was based on two definitions of subject-level response depending on level of %EWL (using the BMI method):

- Observe at least 55% of VBLOC subjects with at least 20% EWL at 12 months.
- Observe at least 45% of VBLOC subjects with at least 25% EWL at 12 months.

The evaluation of this endpoint was based on observed proportions rather than statistical hypothesis tests. Based on the ITT group, neither of these criteria was met, as seen from the summary below:

- 52.5% (85/162, 95% CI: [44.5%, 60.4%]) of VBLOC subjects had at least 20% EWL at 12 months. The observed rate of 52.5% is less than the specified threshold of 55%.
- 38.3% (62/162, 95% CI: [30.8%, 46.2%]) of VBLOC subjects had at least 25% EWL at 12 months. The observed rate of 38.3% is less than the specified threshold of 45%.

Remark: As specified in the protocol, the second co-primary effectiveness endpoint was based on observed proportions in the VBLOC group only. As a supplementary analysis, the analysis of these endpoints has been expanded to include the sham group. The results are summarized in the following bullets:

- Subject-level success defined as %EWL $\geq$ 20%:
  - 52.5% (85/162) in the VBLOC group
  - 32.5% (25/77) in the sham group
  - **Difference: 20.0%, 95% CI: [7.0%, 33.0%]**

- Subject-level success defined as %EWL $\geq$ 25%:
  - 38.3% (62/162) in the VBLOC group
  - 23.4% (18/77) in the sham group
  - **Difference: 14.9%, 95% CI: [2.8%, 27.0%]**

Panel Question: The panel will be asked to discuss whether the second co-primary endpoint results support the effectiveness of the device.

Secondary effectiveness endpoint results

The secondary effectiveness endpoint was %EWL at 12 months after randomization, with ideal body weight determined using the Met Life tables (i.e., using the upper limit of the specified weight range, given a subject's gender and height). As with the first co-primary endpoint, the goal was to show that the VBLOC group %EWL is at least 10% greater than the %EWL in the sham group. As with the first co-primary endpoint, the null and alternative hypotheses are

$$\text{Ho: } \mu_T \leq \mu_C + 10\% \quad \text{vs.} \quad \text{Ha: } \mu_T > \mu_C + 10\%,$$

where μ_T (μ_C) is the mean %EWL in the VBLOC treatment (sham control) group. The test was carried out using a t-test with a significance level of 0.025. The results are similar to those observed for the first co-primary endpoint, as seen in the Table 10.8. The super-superiority goal of 10% was not achieved. Results in the PP group (not shown) are also consistent with these results.

Table 10.8. Results of the analysis for the secondary effectiveness endpoint (%EWL based on the Met Life method) in the ITT group. (NOTE: The mean, min, max and 95% CI values are all %EWL.)

Excess Weight Loss (%)	VBLOC	Sham	Difference
N	162	77	
Mean ± SD	22.2 ± 21.4	14.4 ± 15.9	7.8 ± 19.8
(Min, Max)	(-19.1, 90.6)	(-27.6, 93.4)	
[95% CI]	[18.9, 25.5]	[10.8, 18.0]	[3.0, 12.7]

NOTE: For super-superiority test with 10% margin, p-value=0.380.

Co-morbidities

Additional analyses were performed on co-morbidity measurements (Sections 9.15.5 to 9.15.7 and 9.15.12, volume 22). Although the study did not include a pre-determined endpoint for factors associated with health improvements, data were collected on the 12 month change in parameters such as cholesterol, triglycerides, blood pressure, fasting glucose, and HbA1c. As seen in Table 10.9, there were small improvements of various parameters in both the VBLOC group and the sham group from baseline to 12 months, but the change in the VBLOC group was never statistically significantly different from the change in the sham group.

Table 10.9. Summary of factors associated with co-morbidities at screening, month 12, and changes from screening to month 12.

Parameter	Study Visit	VBLOC mean±SD (N) (min, max)	Sham mean±SD (N) (min,	Difference (VBLOC – Sham)
Systolic Blood Pressure (mmHg)	Screening	127.9 ± 12.5 (162) (98.0, 163.7)	129.9 ± 12.8 (77) (99.3, 167.3)	
	Month 12	121.9 ± 11.8 (147) (83.0, 156.0)	125.5 ± 15.7 (66) (99.0, 182.0)	
	Change	-5.5 ± 14.2 (147) (-50.7, 32.7)	-4.0 ± 13.5 (66) (-32.3, 35.0)	-1.5 ± 14.0 [-5.5, 2.6]
Diastolic Blood Pressure (mmHg)	Screening	80.7 ± 8.8 (162) (56.7, 100.3)	82.3 ± 10.2 (77) (60.7, 109.3)	
	Month 12	77.9 ± 8.1 (147) (51.0, 96.0)	77.1 ± 9.2 (66) (54.0, 93.0)	
	Change	-2.8 ± 9.6 (147) (-23.3, 26.0)	-4.5 ± 8.2 (66) (-27.0, 18.3)	1.7 ± 9.2 [-0.9, 4.2]
Fasting Glucose (mg/dL)	Screening	96.3 ± 17.3 (131) (47.0, 178.0)	98.6 ± 30.0 (55) (72.0, 292.0)	
	Month 12	94.5 ± 15.8 (123) (58.0, 174.0)	97.6 ± 29.9 (51) (70.0, 277.0)	
	Change	-2.0 ± 14.9 (122) (-77.0, 57.0)	-0.6 ± 10.3 (49) (-29.0, 24.0)	-1.4 ± 13.7 [-5.3, 2.6]
HbA1c (%)	Screening	5.7 ± 0.6 (142) (4.5, 8.7)	5.8 ± 1.3 (65) (4.7, 14.3)	
	Month 12	5.3 ± 0.5 (137) (4.5, 7.7)	5.5 ± 1.0 (60) (4.8, 11.8)	
	Change	-0.3 ± 0.4 (135) (-2.3, 0.5)	-0.3 ± 0.5 (60) (-2.5, 0.3)	-0.0 ± 0.4 [-0.2, 0.1]

Table 10.9, continued. Summary of factors associated with co-morbidities at screening, month 12, and changes from screening to month 12.

Parameter	Study Visit	VBLOC mean±SD (N) (min, max)	Sham mean±SD (N) (min, max)	Difference (VBLOC – Sham) mean±SD [95% CI]
Systolic Blood Pressure (mmHg)	Screening	127.9 ± 12.5 (162) (98.0, 163.7)	129.9 ± 12.8 (77) (99.3, 167.3)	
	Month 12	121.9 ± 11.8 (147) (83.0, 156.0)	125.5 ± 15.7 (66) (99.0, 182.0)	
	Change	-5.5 ± 14.2 (147) (-50.7, 32.7)	-4.0 ± 13.5 (66) (-32.3, 35.0)	-1.5 ± 14.0 [-5.5, 2.6]
Diastolic Blood Pressure (mmHg)	Screening	80.7 ± 8.8 (162) (56.7, 100.3)	82.3 ± 10.2 (77) (60.7, 109.3)	
	Month 12	77.9 ± 8.1 (147) (51.0, 96.0)	77.1 ± 9.2 (66) (54.0, 93.0)	
	Change	-2.8 ± 9.6 (147) (-23.3, 26.0)	-4.5 ± 8.2 (66) (-27.0, 18.3)	1.7 ± 9.2 [-0.9, 4.2]
Fasting Glucose (mg/dL)	Screening	96.3 ± 17.3 (131) (47.0, 178.0)	98.6 ± 30.0 (55) (72.0, 292.0)	
	Month 12	94.5 ± 15.8 (123) (58.0, 174.0)	97.6 ± 29.9 (51) (70.0, 277.0)	
	Change	-2.0 ± 14.9 (122) (-77.0, 57.0)	-0.6 ± 10.3 (49) (-29.0, 24.0)	-1.4 ± 13.7 [-5.3, 2.6]
HbA1c (%)	Screening	5.7 ± 0.6 (142) (4.5, 8.7)	5.8 ± 1.3 (65) (4.7, 14.3)	
	Month 12	5.3 ± 0.5 (137) (4.5, 7.7)	5.5 ± 1.0 (60) (4.8, 11.8)	
	Change	-0.3 ± 0.4 (135) (-2.3, 0.5)	-0.3 ± 0.5 (60) (-2.5, 0.3)	-0.0 ± 0.4 [-0.2, 0.1]

<u>Panel question</u>: The panel will be asked to discuss whether the changes in co-morbidities support the effectiveness of the device.

Additional assessments by questionnaire

The following questionnaires were administered to subjects in this trial:

- Impact of Weight on Quality of Life (IWQOL-Lite): A 31-item questionnaire used to assess weight-related quality of life, with possible scores ranging from 0 to 100. Higher scores indicate a higher quality of life.
- Three Factor Eating Questionnaire (TFEQ): A 51-item questionnaire assessing three dimensions (factors) of human eating behavior:
    (i) Cognitive Restraint (measuring efforts to limit food intake), measured on a scale from 0-21, with higher scores reflecting greater constraint.
    (ii) Disinhibition (measuring tendency to lose control over food intake), measured on a scale from 0-16, with lower scores reflecting better ability to control food intake.
    (iii) Hunger (measuring sensations related to hunger), measured on a scale from 0-14, with lower scores reflecting less sensation of hunger.
- Beck Depression Inventory (BDI-II): A 21-item questionnaire to measure the presence of depressive symptoms. Scores range from 0-63, with higher scores reflecting a greater degree of depression. Typically, scores between 0 and 13 represent minimal depression, 14 to 19 reflect mild depression, 20 to 28 reflect moderate depression, and 29 to 63 reflect severe depression. A BDI score of less than 29 was required for inclusion in this trial.

The results obtained on each of these instruments are summarized in Tables 10.10-10.12. In general, both treatment groups showed some improvement on each of these questionnaires, but no significant differences were observed between the treatment groups on any of the questionnaires.

Table 10.10 summarizes the results for the IWQOL-Lite questionnaire. The last row of the table shows the mean changes from baseline to month 12 in each treatment group, as well as the estimated difference between the treatment groups. The observed mean improvements were similar within each treatment group (20.0 points in the VBLOC group, 18.1 points in the sham group), indicating that both groups experienced an increase in quality of life. However, there is no evidence of a difference between VBLOC and sham groups with respect to improvement in quality of life.

Table 10.10. Summary of results from the IWQOL-Lite questionnaire in each treatment group from baseline to month 12.

Study Visit		VBLOC	Sham	Difference Mean ± SD [95% CI]
Screening visit	Mean ± SD (N) (Min, Max)	57.0 ± 16.6 (157) (3.1, 94.5)	54.1 ± 18.4 (77) (14.1, 93.8)	2.9 ± 17.2 [-2.0, 7.8]
Week 12	Mean ± SD (N) (Min, Max)	68.1 ± 14.1 (152) (26.6, 98.4)	65.6 ± 15.8 (72) (18.8, 100.0)	2.5 ± 14.7 [-1.8, 6.8]
6 months	Mean ± SD (N) (Min, Max)	73.9 ± 15.0 (149) (33.6, 100.0)	69.1 ± 16.7 (69) (19.5, 100.0)	4.8 ± 15.6 [0.1, 9.5]
12 months	Mean ± SD (N) (Min, Max)	77.4 ± 13.9 (146) (38.3, 100.0)	70.5 ± 15.7 (63) (5.8, 100.0)	6.8 ± 14.5 [2.3, 11.4]
12 month change	Mean ± SD (N) (Min, Max)	20.0 ± 17.5 (142) (-27.3, 76.6)	18.1 ± 17.7 (63) (-29.3, 60.9)	1.9 ± 17.6 [-3.4, 7.2]

Table 10.11 summarizes the improvements in the three dimensions of the TFEQ from baseline to month 12. For the first factor (Cognitive Restraint), both VBLOC and sham groups experienced an increase from baseline to month 12, which means there was improved self-restraint in limiting food intake. For the second factor (Disinhibition), both groups had a decrease from baseline to month 12, which means that subjects were less likely to lose control over food intake (i.e., less likely to overeat or binge eat). For the third factor (Hunger), the scores in both groups improved from baseline to month 12, reflecting a decrease level of hunger. While both VBLOC and sham groups enjoyed some level of improvement for all three factors, only hunger (Factor 3) showed significant difference between the groups.

Table 10.11. Summary of the changes in the three dimensions (or factors) of the Three Factor Eating Questionnaire.

Factor 1: Cognitive Restraint [Possible scores: 0-21]

Study Visit		VBLOC	Sham	Difference Mean ± SD [95% CI]
Screening visit	Mean ± SD (N) (Min, Max)	9.5 ± 4.4 (160) (1.0, 20.0)	9.2 ± 4.2 (77) (1.0, 19.0)	0.3 ± 4.3 [-0.9, 1.4]
12 months	Mean ± SD (N) (Min, Max)	15.2 ± 4.2 (146) (1.0, 21.0)	14.9 ± 4.1 (64) (2.0, 21.0)	0.3 ± 4.1 [-0.9, 1.5]
12 month change	Mean ± SD (N) (Min, Max)	5.8 ± 4.7 (145) (-12.0, 16.0)	5.3 ± 4.5 (64) (-3.0, 16.0)	0.5 ± 4.6 [-0.8, 1.9]

Factor 2: Disinhibition [Possible scores: 0-16]

Study Visit		VBLOC	Sham	Difference Mean ± SD [95% CI]
Screening visit	Mean ± SD (N) (Min, Max)	10.3 ± 3.3 (160) (2.0, 16.0)	10.1 ± 3.3 (77) (3.0, 15.0)	0.3 ± 3.3 [-0.6, 1.2]
12 months	Mean ± SD (N) (Min, Max)	7.0 ± 3.8 (146) (1.0, 16.0)	8.1 ± 3.9 (64) (1.0, 16.0)	-1.0 ± 3.8 [-2.2, 0.1]
12 month change	Mean ± SD (N) (Min, Max)	-3.3 ± 3.7 (145) (-13.0, 6.0)	-2.4 ± 3.7 (64) (-10.0, 9.0)	-1.0 ± 3.7 [-2.1, 0.1]

Factor 3: Hunger [Possible scores: 0-14]

Study Visit		VBLOC	Sham	Difference Mean ± SD [95% CI]
Screening visit	Mean ± SD (N) (Min, Max)	8.0 ± 3.3 (160) (1.0, 14.0)	7.9 ± 3.8 (77) (0.0, 14.0)	0.1 ± 3.4 [-0.9, 1.1]
12 months	Mean ± SD (N) (Min, Max)	3.9 ± 3.3 (146) (0.0, 12.0)	5.3 ± 4.1 (64) (0.0, 14.0)	-1.4 ± 3.6 [-2.5, -0.2]
12 month change	Mean ± SD (N) (Min, Max)	-4.1 ± 3.9 (145) (-13.0, 4.0)	-2.8 ± 4.3 (64) (-13.0, 7.0)	-1.3 ± 4.0 [-2.5, -0.0]

The results from the Beck Depression Inventory (BDI-II) are summarized in the Table 10.12. On average, baseline scores reflected minimal symptoms of depression, with a further decrease at month 12 of 3.4 points in the VBLOC group and 3.0 points in the sham group. There is no evidence of a difference between VBLOC and sham groups with respect to improvement in depression scores.

Table 10.12. Summary of the scores from the BDI-II in each treatment group from baseline to month 12.

Study Visit		VBLOC	Sham	Difference Mean ± SD [95% CI]
Screening visit	Mean ± SD (N) (Min, Max)	9.1 ± 7.1 (159) (0.0, 28.4)	9.4 ± 6.1 (77) (0.0, 28.0)	-0.3 ± 6.8 [-2.1, 1.4]
Week 12	Mean ± SD (N) (Min, Max)	6.2 ± 6.0 (153) (0.0, 36.0)	6.8 ± 6.1 (72) (0.0, 34.0)	-0.6 ± 6.0 [-2.3, 1.1]
6 months	Mean ± SD (N) (Min, Max)	5.7 ± 5.2 (150) (0.0, 28.0)	6.3 ± 7.6 (69) (0.0, 31.0)	-0.6 ± 6.1 [-2.6, 1.4]
12 months	Mean ± SD (N) (Min, Max)	5.6 ± 6.1 (146) (0.0, 31.0)	6.8 ± 7.8 (64) (0.0, 38.0)	-1.2 ± 6.6 [-3.4, 0.9]
12 month change	Mean ± SD (N) (Min, Max)	-3.4 ± 7.9 (144) (-27.0, 21.0)	-3.0 ± 7.7 (64) (-19.0, 21.0)	-0.4 ± 7.9 [-2.7, 1.9]

Blinding assessments

Subjects completed blinding assessments at week 1, month 6, and month 12. In each blinding assessment, subjects were asked to indicate the VBLOC group to which they thought they had been randomized. Possible responses were “Treatment group”, “Control group” or “Don’t know/no guess”. The results from these blinding assessments are shown in Table 10.13 below. At week 1, about half of the VBLOC group subjects (53.5%) guessed they were in the VBLOC group, while only 4.0% of sham group subjects correctly guessed their group. At month 6, the proportion of correct guesses improved to 72.8% in the VBLOC group and 35.3% in the sham group. At month 12, the proportion of correct guesses was 74.7% in the VBLOC group and 51.5% in the sham group, reflecting continuing uncertainty in the sham group about the treatment received.

Table 10.13. Summary of the blinding assessments conducted at week 1, month 6, and month 12.

Randomization Guess	VBLOC	Sham
1 week	N=157	N=75
VBLOC group	84 (53.5%)	29 (38.7%)
Sham group	8 (5.1%)	3 (4.0%)
Don't know/no guess	65 (41.4%)	43 (57.3%)
6 months	N=147	N=68
VBLOC group	107 (72.8%)	22 (32.4%)
Sham group	13 (8.8%)	24 (35.3%)
Don't know/no guess	27 (18.4%)	22 (32.4%)
12 months	N=146	N=66
VBLOC group	109 (74.7%)	10 (15.2%)
Sham group	13 (8.9%)	34 (51.5%)
Don't know/no guess	24 (16.4%)	22 (33.3%)

11. SAFETY ASSESSMENT

The primary safety endpoint is the rate of serious adverse events (SAEs) related to implant or revision procedures, device, or therapy in the VBLOC group through 12 months of follow-up. The goal of the analysis was to show that this SAE rate is less than a pre-specified performance goal of 15%. The null and alternative hypotheses for this endpoint can be stated as

$$\text{Ho: } \pi_T \geq 15\% \quad \text{vs.} \quad \text{Ha: } \pi_T < 15\%,$$

where π_T is the SAE rate in the VBLOC group at 12 months, as described above.

Table 11.1 presents the SAEs through month 12. Among the 162 subjects randomized to the VBLOC group (i.e., the intent-to-treat group), there were 6 SAEs identified as related to implant or revision procedures, device, or therapy, which leads to an observed rate for the primary safety endpoint of 3.7% (6/162, 95% CI: [1.4%, 7.9%]). Since the upper bound of this interval is less than 15%, this result meets the primary safety endpoint.

The second row in Table 11.1 indicates there were 9 subjects who had SAEs related to the general surgical procedure. These events were not counted as part of the primary safety endpoint, which included SAEs related to the implant procedure, device, or therapy. FDA has performed an additional analysis of the primary endpoint by including the 9 subjects with SAEs classified as general surgical procedure. In this analysis, there are 15 SAEs in 14 subjects (one subject had two SAEs), so the updated SAE rate based on the ITT group is 8.6% (14/162), with a 95% CI of [4.8%, 14.1%], which meets the performance goal of 15%.

The addition of the SAEs related to the general surgical procedure was discussed in the 100-day meeting with EnteroMedics on October 16, 2013. EnteroMedics has since indicated that they do not believe that these additional SAEs should be added to the primary safety endpoint, but that this SAE information would be included in device labeling to inform physicians and patients of the overall risk posed by the device and the surgical procedure.

Table 11.1. Serious adverse events through month 12 by origin (as determined by Clinical Events Committee) and VBLOC group.

SAE Origin	VBLOC		Sham	
	N subjects (%)	N events	N subjects (%)	N events
Device	3 (1.9%)	3	0 (0.0%)	0
General surgical procedure	9 (5.6%)	9	0 (0.0%)	0
Implant/revision procedure	2 (1.2%)	2	0 (0.0%)	0
Other/Not related	4 (2.5%)	5	2 (2.6%)	2
Therapy algorithm	1 (0.6%)	1	0 (0.0%)	0
Pre-existing condition	6 (3.7%)	6	2 (2.6%)	2

NOTE: The highlighted rows in this table show the 6 SAEs that contributed to the primary safety endpoint analysis.

Panel question: The panel will be asked to discuss whether the primary safety endpoint results support the safety of the device.

Through 18 months, there has been one additional device-related SAE in the VBLOC group, so the rate is 4.3% (7/162, 95% CI: [1.8%, 8.7%]) in the ITT population. Including those 9 SAEs related to the general surgical procedure, the rate is 9.3% (15/162, 95% CI: [5.3%, 14.8%]). There have been no deaths or unanticipated adverse device effects (UADEs) with the device.

Demographics

The Maestro ReCharge Pivotal Trial had an enrollment of 162 subjects randomized to receive VBLOC therapy and 77 subjects randomized to a sham group. Among the VBLOC subjects, 157 (97%) subjects we implanted with the device, 147 (91%) subjects completed the 12 month visit and 117 (72%) subjects completed the 18 month visit. Among the sham control subjects, 76 (99%) subjects were implanted with the device, 66 (86%) subjects completed the 12 month visit and 42 (54%) subjects completed the 18 month visit. The overall follow-up rate among the enrolled 239 subjects was 89% (213 of 239) at 12 months and 67% (159 of 239) at 18 months. There were 5 VBLOC subjects that did not receive an implant that included 3 subjects that did not meet exclusion criteria, 1subject that did not meet exclusion criteria and was a failure to implant and 1 subject that was based on the principal investigator decision in a patient identified with delayed gastric emptying. There was 1 sham control subject that did not receive an implant based on a personal decision.

Serious Adverse Events (SAEs)

There were a total of 16 related serious adverse events (SAEs) that occurred through 18 months. All of the related SAEs were among the VBLOC subjects. Among the VBLOC subjects, 8.6% (14 of 162) experienced an SAE through 12 months, and 9.6% (15 of 162) of the subjects through 18 months. This additional subject had a gastric perforation related to a device explant as discussed below. Table 11.2 provides the VBLOC subject SAEs categorization.

Table 11.2. Serious adverse events through 12- and 18-months by relatedness

SAEs	VBLOC Subjects	Events
General surgery related through 12 months	9	9
Device related through 12 months		
Neuroregulator malfunction	2	2
Pain at neuroregulator site	1	1
Implant/revision related through 12 months		
Atelectasis following the initial implantation surgery	1	1
Emesis/vomiting	1	1
Therapy related through 12 months		
Gallbladder disease	1	1
Total through 12 months	14 (8.6%, 95% CI: 4.8%, 14.1%)	15
Implant/revision related between 12 to 18 months		
Gastric perforation related to device removal	1	1
Total through 18 months	15 (9.3%, 95% CI: 5.3%, 14.8%)	16

General Surgical Procedure Related SAEs

The 9 VBLOC subjects with SAEs related to the initial surgery were described as follows:

1. Subject developed post-operative coughing and nausea. The subject required an overnight hospitalization.
2. Subject developed post-operative nausea which was treated with intravenous metoclopramide. The subject required an overnight hospitalization.
3. Subject was noted to have 'oozing' during the surgery without any evidence of hemodynamically significant bleeding. The subject required an overnight hospitalization.
4. Subject with a history of Hepatitis C was noted at the time of surgery to have liver cirrhosis. During the retraction of the liver a small laceration occurred. Intraoperative liver biopsies were performed. There were problems controlling the bleeding from both the laceration and the biopsy sites, which was ultimately controlled. The placement of the neuroregulator and leads was aborted. An abdominal CT scan demonstrated a significant intra-abdominal hematoma. The subject required 2 units of packed red blood cells, and a 3 day hospitalization.
5. Subject developed post-operative nausea associated with abdominal distention and epigastric fullness. An abdominal X-ray demonstrated a moderate ileus. The subject required a 2 day hospitalization.

6. Subject developed post-operative nausea with dry heaves and abdominal pain which was treated with a patient controlled analgesia pump. The subject required a 3 day hospitalization.
7. Subject developed post-operative nausea, vomiting and abdominal pain. The subject required an overnight hospitalization.
8. Subject developed post-operative nausea, abdominal pain and lightheaded with ambulation. The subject required a 2 day hospitalization. The CEC noted "It is not clear if the device was active at the time" but EMI has confirmed that the device was active.
9. Subject developed post-operative nausea, vomiting and headache. The subject required an overnight hospitalization.

Device Related SAEs (through 12 months)

- 1 SAEs related to pain at the neuromodulator site.
- 2 SAEs related to neuroregulator malfunction

Implant/revision Related SAEs (through12 months)

- atelectasis following the initial implantation surgery which was thought to be facilitated by splinting due to pain.
- emesis/vomiting that was aggravated by the initial implant procedure which resulted in evulsion of the stomach into the chest requiring surgical repair.

Therapy Related SAEs (through 12 months)

- gallbladder disease

Implant/revision Related SAEs (between 12 and 18 months)

- gastric perforation occurred during an elective removal of the device

EMI provided the CEC summary of the clinical presentation of the subject with the gastric perforation. This was a 29 year old woman with a past history of two C-sections, a cholecystectomy, a tubal ligation and uterine ablation that had the placement of a neuroregulator on 12/14/2011. She elected to have the device removed, which was performed as an outpatient on 2/12/2013. Overnight following the procedure, she experienced increasing abdominal pain associated with nausea and vomiting. She presented to the emergency room the following day quite ill with marked abdominal pain, bilateral shoulder pain a systolic blood pressure of 87, a pulse of 116, a creatinine level of 3.2. An abdominal CT scan showed a moderate amount of free fluid in the abdomen. She was taken to the OR where a 1.8 cm gastric perforation was identified at the gastroesophageal junction. The perforation was primarily repaired, and the area was reinforced with omentum which was sutured over the site of the repair. She remained mechanically ventilated overnight and required vasopressors to maintain her blood pressure. She improved post-operatively. Her creatinine level returned to normal, and she was extubated the on the 1st post-operative day. She also had a transient febrile episode. She continued to improve and was discharged to home 6 days after her initial explantation surgery (5 days after the repair of the gastric perforation).

According to EMI, this is the first occurrence of gastric perforation in over 640 implants of any generation of the Maestro System worldwide. EMI also notes that the source documentation from the surgeon states that the perforation was on the anterior gastric wall near the gastroesophageal junction.

MR Unsafe

This device is a permanent implant, and is labeled MR unsafe. If a user needs an MRI examination after the device is implanted, it may be necessary to explant the device. According to EMI, in less than 5% of cases of explant, the distal portion of the electrode and a small length of lead body (<5 cm) remained behind due to extensive fibrosis around the implant.

Panel question: The panel will be asked to discuss the safety implications of the device being MR unsafe.

Unrelated SAEs

There were an additional 7 SAEs that were not felt to be related to the device, procedure, or therapy or related to pre-existing conditions that all occurred through 12 months. Among the VBLOC subjects, these included 1 subject each with incidental gastroenteritis, abdominal pain, colitis-nausea, vomiting and severe abdominal pain, an allergic reaction and gallbladder disease. Among the sham control subjects, these included 1 subject each with gastritis related to NSAID use and breast cancer.

ReCharge Study: Adverse Events (AEs)

There were 377 adverse events (AEs) that were device, procedure, or therapy related among 134 (83%) VBLOC subjects and 94 AEs among 53 (69%) sham control subjects through 12 months. There were a total of 419 AEs that were device, procedure or therapy related among 139 (86%) VBLOC subjects and 96 AEs in among 53 (69%) sham control subjects through 18 months. The most common related VBLOC and sham control subject AEs through 12 and 18 months are summarized in Tables 11.3 and 11.4.

Table 11.3. Most common device, implant/revision procedure, or therapy related AEs through 12 months

AE Type	VBLOC (n=157)		Sham (n=76)	
	Subjects	Events	Subjects	Events
Neuroregulator site pain	59 (38%)	69	31 (42%)	32
Other pain	37 (23%)	42	0 (0%)	0
Heartburn/dyspepsia	35 (22%)	39	3 (4%)	3
Other	34 22%)	43	7 (9%)	10
Abdominal Pain	20 (13%)	26	2 (3%)	2
Dysphagia	13 (8%)	13	0	0
Eructation/belching	12 (5%)	12	0	0
Nausea	11 (7%)	14	1 (1%)	1
Chest pain	9 (6%)	9	2 (3%)	2

Table 11.4. Most common device, implant/revision procedure, or therapy related AEs through 18 months

AE Type	VBLOC (n=157)		Sham (n=76)	
	Subjects	Events	Subjects	Events
Neuroregulator site pain	59 (38%)	69	31 (42%)	32
Other pain	37 (23%)	42	0 (0%)	0
Heartburn/dyspepsia	35 (22%)	39	3 (4%)	3
Other	34 22%)	43	7 (9%)	10
Abdominal Pain	20 (13%)	26	2 (3%)	2
Dysphagia	13 (8%)	13	0	0
Eructation/belching	12 (5%)	12	0	0
Nausea	11 (7%)	14	1 (1%)	1
Chest pain	9 (6%)	9	2 (3%)	2

Additional information is provided on specific types of adverse events that were observed through 12 months.

Dysphagia

13 (8.3%) of subjects (13 events).

12 events were reported as mild and 1 was reported as moderate.

Dysphagia developed within the first few weeks following implantation in all but one of the reported instances.

No intervention was necessary in 10 of the 13 cases.

One subject with late onset dysphagia resolved with medication intervention, one subject was treated with

therapy adjustment and one was advised to chew food carefully.

Nausea
11 (7.0%) subjects (14 events).
7 events were reported as mild, 5 were reported as moderate and 2 were reported as severe.
All of the moderate or severe events occurred within days of the implant or revision procedure.
5 of the moderate to severe nausea episodes resulted in prolongation of hospitalization after implantation and were classified as SAEs.
3 of the post-operative mild nausea AEs required of therapy algorithm adjustments.
All nausea AEs resolved.

Abdominal Pain
20 (12.3%) subjects (26 events).
17 events reported as mild and 9 events reported as moderate
Described as epigastric pain, "band around the stomach," abdominal pain after eating, gas pain and rippling in abdomen.
Adjustment with ramp and/or current amplitude was effective in reducing the sensations in 18 events.
4 of the mild and 1 moderate events were ongoing as of the 12-month visit.

Pain – Other
37 (22.8%) subjects (42 events).
28 events reported as mild, 14 reported as moderate, and none were reported as severe.
Pain in the roof of the mouth, epigastric area, esophagus, ear, pain with overeating, pain at ramp-up and/or intermittent pain.
Interventions included 17 therapy algorithm changes and 8 medication changes.
8 of the mild and 6 of are moderate AEs were ongoing as of the 12-month visit.

AEs of uncertain etiology
There were several non-gastrointestinal AEs that were of uncertain etiology. This included subjects with bradycardia, lightheadedness and cardiac abnormalities, as described in further detail, below.

There were 3 subjects that had episodes of bradycardia through 18 months (with none in the sham control group). Two events were considered by the investigator as possibly related to therapy, and one was of unknown relatedness.

One subject had a heart rate on the screening ECG of 78 bpm. At the 4-month visit, the ECG heart rate was 50 bpm, although the pulse rate was 80. The most recent neuromodulator modification was at the month 1 visit to the recommended 6 mA amplitude. No additional recorded pulse rates or ECG heart rates were below 60. The AE was considered by the investigator to be of unknown relationship to the device or therapy.

One subject had a heart rate by ECG at the screening visit of 67 bpm. On multiple occasions during the study, the pulse rate was noted to be between 51 and 60 bpm. No changes to the neuromodulator settings were made at or near the onset of the AE, and the settings were not changed as a result of the AE. The investigator considered the AE to be possibly related to therapy.

One subject had a pulse rate of 71 bpm, and the heart rate by ECG of 59 bpm. Bradycardia was reported as an AE at the 4-month visit, based on an ECG heart rate of 59 bpm, although pulse rate at that visit was 71 bpm. An ECG heart rate of 57 and 58 bpm were recorded at the 8 and 12 month visits, although the corresponding pulse rates were 78 and 70 bpm. The neuromodulator settings were unchanged following the 4-month visit. The AE was considered by the investigator to be possibly related to therapy.

There were 2 subjects that had episodes of lightheadedness through 18 months.

One subject had onset of lightheadedness approximately 3 weeks after implantation. The lightheadedness was reported as related to moving around. The pulse rate and ECG heart rates were all >60 bpm, and the ECG showed a sinus rhythm. The AE resolved without any intervention after approximately 1 week. The cause of the lightheadedness was unknown.

One subject had onset of lightheadedness reported at the 16 month visit, associated with swinging around quickly. The pulse rate and ECG were normal. The lightheadedness resolved within approximately 2 weeks. No neuromodulator setting adjustments were performed during this time period.

There were 5 AEs related to cardiac abnormalities, of which 1 was considered to be possibly related to therapy.

Sinus bradycardia, sinus arrhythmia and a heart rate of 47 bpm was identified on an ECG at the 4 month visit. No neuromodulator setting adjustments had been made during this period. An evaluation by the subject's primary care physician determined that these abnormalities were related to the subject's pre-existing medications. The AE was considered to be unrelated to the device or therapy.

Subject Withdrawals

There were a total of 33 subject withdrawals through18 months. Of the 20 VBLOC subjects that were withdrawals, 3 were AE-related; of the 13 sham control subject withdrawals, 6 were AE-related. The AEs related to withdrawals are as follows:

20 VBLOC subject withdrawals (13%), 2 AE-related (1%)

- Pain at the neuroregulator site

- Heartburn and dyspepsia (between 12 and 18 months)
- Gastric perforation (between 12 and 18 months)

13 Sham control subject withdrawals (17%), 6 AE-related (8%)

- Anxiety related symptoms
- Breast cancer diagnosis
- Pain at neuromodulator site
- Need for MRI examination (between 12 and 18 months)
- Pain at neuromodulator site
- Worsening IBS symptoms (between 12 and 18 months)

Surgical Revisions

There were 8 VBLOC subjects that underwent 9 surgical revisions of the devices through 12 months and an additional 3 VBLOC subjects between 12 and 18 months. No sham control subjects required a surgical revision. The reasons for the surgical revisions are as follows:

9 VBLOC surgical revisions through 12 months (5%)

- 4 related to pain at the neuromodulator site (AEs), including 1 subject with a neuromodulator 'tilt'
- 4 related to device malfunction
- 1 related to an asymptomatic neuromodulator 'tilt'

3 VBLOC surgical revisions between 12 and 18 months (2%)

- 2 related to pain at the neuromodulator site (AEs)
- 1 related to device malfunction

Surgical Explants

There were 13 total surgical explants performed through 12 months and an additional 23 subjects between 12 and 18 months. The AEs related surgical explants are as follows:

13 total surgical explants through 12 months

5 VBLOC subjects (2 AE related)

- Jabbing pain when doing physical activity
- Heartburn symptoms

8 Sham subjects (4 AE related)

- Shoulder pain that required an MRI
- Worsening of IBS symptoms
- Breast cancer diagnosis
- Pain at neuromodulator site

23 total surgical explants between 12 and 18 months

14 VBLOC subjects (2 AE related)

- Right upper quadrant abdominal pain
- Right arm pain which required an MRI

9 Sham subjects (2 AE related)

- Worsening back and neck pain which required an MRI
- Intermittent abdominal discomfort the neuroregulator site

Panel Questions:
The panel will be asked to discuss any additional safety concerns.

12. POST APPROVAL STUDY CONSIDERATIONS

Applicant's PAS proposal

A. Objectives

EnteroMedics proposes to use the 5-year data from subjects who were originally randomized to the VBLOC arm and crossover subjects from those originally randomized to the sham control group to support the long-term performance and safety of the MAESTRO Rechargeable System in the post-approval setting.

B. Study Design and Study Population

The PAS is an extended 5-year follow-up of all subjects who received the MAESTRO device in the ReCharge premarket study, including those who were randomized to the VBLOC arm and sham subjects who 'crossed-over' at 12 months follow-up.

C. Hypothesis and Sample Size

The primary safety objective of the PAS will be to show that the rate of serious adverse events (SAEs) related to the device, implant/revision procedure, general surgical procedure, or therapy is statistically lower than and objective performance criterion (OPC) of 25% (expected rate of 15% with a 10% margin) at 5 years.

Assuming a 25% OPC, one-sided 0.05 type-I error rate, expected 5-year related SAE rate of 15%, and an 8% rate of censoring per year from implant/crossover (40% attrition over 5 years),

and the anticipated pooled sample size of 162 randomized VBLOC subjects with 30-40 crossover subjects, it was estimated that the hypothesis would be powered at the 80% level.

D. Enrollment Plan and Follow-up

The ReCharge trial is a 5-year study. The first 12 months of follow-up data were included in the premarket submission, and years 2 to 5 will be part of the post-approval study. Therefore, there will be no new enrollment of study subjects or clinical sites specifically for the PAS.

All subjects will be followed for 5 years post-implant/cross-over. After the 17 visits in the first year, subjects will be seen monthly through 2 years post-implant/cross-over, and then every two months through 5 years.

E. Study Endpoints

The primary safety endpoint is SAEs related to the device, implant/revision procedure, general surgical procedure, or therapy at 5 years.

The effectiveness endpoints are percentage excess weight loss (%EWL) and percentage total body weight loss (%TBL).

F. Statistical Plan

The primary safety objective of the PAS will be to show that the rate of SAEs related to the device, implant/revision procedure, general surgical procedure, or therapy is statistically lower than 25% at 5 years. The hypothesis test will be evaluated using the Kaplan- Meier estimate of the SAE rate at 5 years. Subjects will be censored at the time of their first related SAE or last available follow-up. The endpoint will be met if the upper 95% log-log CI is lower than 25% at 5 years.

The effectiveness endpoints will be assessed using mixed effects regression models. Both the estimated mean and 95% confidence intervals for %EWL and %TBL will be reported by visit using this methodology to reflect uncertainty for missing data. In addition to the mixed effects model, data will be reported as observed without imputation. Weight loss will also be reported pooled and stratified by original VBLOC randomized group versus crossover group.

<u>FDA Assessment of Applicant's PAS Proposal</u>

1. Long-term evaluation of the safety and effectiveness of MAESTRO is an appropriate objective for this PAS and an extended follow-up of the premarket cohort is a reasonable approach for meeting this objective.

2. Enrollment for the proposed PAS is complete, as all subjects for the PAS were enrolled in the 5-year premarket study. FDA believes that a follow-up duration of 5 years is sufficient since patients with a BMI of at least 40 kg/m2 or a BMI of at least 35 kg/m2 with one or more obesity-related comorbidities are likely to be older compared to those on the lower end of the BMI spectrum. However, the panel will be asked if 5 years of follow-up is sufficient to evaluate the long-term performance of MAESTRO.

3. There is some concern about whether a sufficient number of subjects will be active at the end of the 5-year study to perform the hypothesis testing. EMI performed a sample size calculation with an assumption of 35-40% attrition, which FDA believes is too high. With a high attrition rate, there is a concern that the subset of study participants who have completed the 5-year follow-up are not representative of all subjects who began the study. For this reason, a follow-up rate of at least 80% (20% attrition) would be considered more appropriate.

4. EMI proposes to assess device effectiveness by %EWL and %TBL, and device safety by the 5-year rate of SAEs related to the device, implant/revision procedure, general surgical procedure, or therapy. These outcomes are appropriate for evaluating the long-term effectiveness and safety, respectively, of MAESTRO.

5. The proposed hypothesis test for the 5-year related SAE rate is acceptable for the long-term safety evaluation. The OPC of 25% (with an expected rate of 15% plus a 10% margin) is also acceptable. However, use of the term "Objective Performance Criterion" is not appropriate in this case because this terminology is generally reserved for instances where there is sufficient, historical data to support a defined threshold. MAESTRO is a 1st of a kind device that has yet to be well-described in the literature. Therefore, the term "Performance Goal" is more appropriate to describe the 25% threshold for related SAEs.

Panel Questions: The panel will be asked to discuss the PAS, including the duration of the study and the proposed study endpoints.

13. TRAINING CONSIDERATIONS

EMI has developed a comprehensive training program which has specific guidelines for selecting centers that have adequate experience, facilities, programs and support staff, including surgeons and clinicians. Once a center is selected, it is certified based on defined criteria and then certification is documented. After center certification, training and certification of the support staff commences.

Surgeon selection at the center is done based on defined criteria. Surgeon training consists of both implant training, including a certification process, and explant training including a certification process. Implant and explant training can either be conducted during the same training session, or separately. The surgeon implant training program consists of classroom training, observation, a proctored implant and review by a surgeon trainer of the first few implants before certification is granted and documented. Implant training certification expires one year after either issue of certification or completion of most recent implant procedure, whichever comes later. The surgeon will be required to be recertified to continue to implant the MAESTRO Rechargeable System.

Surgeon explant training consists of classroom training, surgical technique review and a proctored explant by a surgeon trainer before certification is granted and documented. Explant training certification expires one year after either issue of certification or completion of most recent explant procedure, whichever comes later. The surgeon will be required to be recertified to continue to explant the MAESTRO Rechargeable System.

Concurrently, clinicians are trained and certified to support the MAESTRO Rechargeable System intra-operatively and post-operatively. Intraoperative clinicians are classroom trained on the equipment setup, registration, intraoperative programming and performance testing of the MAESTRO Rechargeable System. They must complete a supervised case demonstrating their understanding of the system before they are certified as an Intraoperative clinician. Documentation of this certification is done. Postoperative clinicians are trained on the equipment for not only their administration, including programming and reporting, but also to demonstrate to the patient how to interact with the applicable components of the MAESTRO Rechargeable System. Postoperative clinicians must demonstrate proficiency to the trainer before they are certified.

VBLOC Certified Center (VCC) Qualifications:

- VCC has performed over 200 foregut procedures
- Provides a variety of bariatric surgical options to patients
- Experienced surgeon (s):

- Experience in laparoscopic surgery (performed at least 125 bariatric operations)
- Experience in surgery of gastro-esophageal junction (such as in surgical correction of reflux disease)
- Demonstrated ability to suture laparoscopically, including intra-corporeal knot tying
- Enrollment in a relevant national professional organizations (i.e. American Society of Metabolic and Bariatric Surgery (ASMBS), International Federation for the Surgery of Obesity (IFSO), SAGES, ACS, etc.)
    - A support team on hand, including, for example:
- Surgeons
- Clinicians and nurses

- Nutritionists, or dieticians
- Psychologists
- Exercise physiologist
    - Patient follow-up program, including, for example:
- Patient diet and lifestyle modification plan
- Regular patient follow-up protocols
- Patient tracking and monitoring capabilities
- Support groups
- Commitment to long-term follow-up of patients
    - Quality control program to effectively measure best practices and track quality of care and outcomes.
    - Appropriate equipment and facilities

Once EnteroMedics or its Agent determines that the VCC has met the necessary criteria, EnteroMedics or its Agent will certify the VCC and document this certification on the VBLOC Certified Center (VCC) Certification Form.

After the VCC has been certified, training and certification of the surgeon and support staff (clinicians, etc.) can commence and appropriately documented prior to any materials, equipment or products shipping to the VCC.

The VCC will be responsible for maintaining records and keeping surgeon certification current. Surgeon certification expires 12 months from the date the Surgeon Certification Training Program - Surgical Implantation of the MAESTRO Rechargeable System Certification Form was completed or the surgeon's last MAESTRO Rechargeable System implant, whichever is later. Surgeons that have previously undergone training will be need to be recertified by reviewing updates that may have occurred since completion of their initial certification to surgical technique, clinical results, or the MAESTRO Rechargeable System. The

VCC should contact EnteroMedics or EnteroMedics' Agent for re-certification.

14. LABELING CONSIDERATIONS

Device labeling is provided for MAESTRO Rechargeable System Components; Accompanying Labeling Summary by Component; System Instructions for Use; Surgical Implant Procedure Manual; Clinician Program Manual; Patient Instructions; Patient Easy Charge Guide; Patient Registration and Temporary Identification; Patient Identification Labels, and; Device Labels.

The Patient Labeling discusses improvements in obesity risk factors in patients who received VBLOC therapy, including an analysis of cardio-metabolic parameters (e.g., levels of HbA1c, plasma cholesterol levels) in the VBLOC subjects, and a sub-group of (sham) subjects who achieved ≥ 20% EWL. However, the information provided in the labeling did not compare results of risk factor improvements achieved with VBLOC therapy versus sham subjects who achieved ≥ 20% EWL.

Panel Questions: The panel will be asked to discuss any concerns about the proposed labeling.

15. SUMMARY

Obesity is a chronic and debilitating condition, for which diet and exercise alone are often ineffective in reducing weight. The MAESTRO Rechargeable System is a permanent, implantable device that provides electrical stimulation to the abdominal vagus nerve for patients seeking clinically significant weight loss.

EnteroMedics Inc. conducted the ReCharge pivotal study, a prospective, randomized (2:1), double-blind, sham-controlled, multi-center trial to evaluate the safety and effectiveness of the Maestro system in treating obesity. The trial enrolled subjects who had a BMI 40-45 kg/m^2 or a BMI 35-39.9 kg/m^2 with at least one obesity-related co-morbid condition, and who had failed a more conservative weight reduction alternative. Enrollment of subjects with type 2 diabetes was limited to 10% (with no more than 3 such subjects per center).

A total of 239 subjects were enrolled at 10 investigational sites; 162 subjects were randomized to the device group, and 77 were randomized to the sham control group. Subjects randomized to the sham control group underwent a surgical procedure consisting of anesthesia, implantation of a non-functional neuroregulator, and the same number of incisions an investigator would use during the laparoscopic placement of the leads.

The study had two co-primary effectiveness endpoints, both of which were not met, and a primary safety endpoint which was met.

The first co-primary endpoint specified that the device would achieve a mean percent excess weight loss (%EWL) that was at least 10% greater than the sham mean %EWL. The average %EWL at 12 months was 24.4% (SD=23.6%) in the VBLOC group and 15.9% (SD=17.7%) in the sham group, resulting in an average difference between the VBLOC and sham groups of 8.5% (95% CI: [3.1%, 13.9%]). While the average %EWL was higher in the VBLOC group than in the sham group, the pre-specified superiority margin of 10% was not achieved.

EnteroMedics also provided 18 month data for %EWL. These data were limited because of incomplete follow-up (follow-up rates of 72.2% and 54.5% in the VBLOC and sham groups, respectively), and breaking of the blind in the sham group after 12 months (most subjects were unblinded at the 16 month visit or after). At 18 months, the observed mean %EWL in the VBLOC group was 25.2% (95% CI: [20.6, 29.8]) and 11.7% (95% CI: [5.4, 18.0]) in the sham group, resulting in a treatment difference of 13.5% (95% CI: [5.7, 21.3]).

The second co-primary effectiveness endpoint had two requirements: (i) at least 55% of VBLOC subjects needed to achieve a %EWL of at least 20%; and (ii) at least 45% of VBLOC subjects needed to achieve a %EWL of at least 25%. The assessments of these objectives were based on observed rates rather than statistical hypothesis tests, and according to the protocol both of these objectives should be met for trial success. Neither of the co-primary objectives was met: (i) 52.5% (<55%) of VBLOC subjects had a %EWL of at least 20%; (ii) 38.3% (<45%) of VBLOC subjects had a %EWL of at least 25%.

The primary safety endpoint of the ReCharge trial was to demonstrate that the 12-month serious adverse event (SAE) rate related to implant or revision procedures, device, or therapy was less than a performance goal of 15% among the subjects in the VBLOC group. There were 6 SAEs identified in these categories, which led to an observed SAE rate of 3.7% (6/162, 95% CI: [1.4%, 7.9%]) among the VBLOC subjects, which met the primary safety endpoint, because the upper bound of this confidence interval is less than 15%. There were also 9 subjects who had SAEs related to the general surgical procedure. When these SAEs were counted as part of the primary safety endpoint, using an intent-to-treat analysis, the updated SAE rate was 8.6% (14/162), with a 95% CI of [4.8%, 14.1%], which also meets the performance goal of 15%.

The panel will be asked to discuss these and other aspects of the MAESTRO Rechargeable System and the ReCharge pivotal study. The panel should consider the totality of the data in its assessment of the safety and effectiveness of the device.

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